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(54) Title: NOVEL POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

(57) Abstract

The present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

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NOVEL POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

FIELD OF THE INVENTION

The present invention relates generally to the identification and isolation of novel DNA and to the recombinant production of novel polypeptides encoded by that DNA.

BACKGROUND OF THE INVENTION

Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

Membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process,

can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins.

We herein describe the identification and characterization of novel secreted and transmembrane polypeptides and novel nucleic acids encoding those polypeptides.

1. PRO213

Human growth arrest-specific gene 6 (gas6) encodes a protein that is expressed in a variety of different tissues and which has been reported to be highly expressed during periods of serum starvation and negatively regulated during growth induction. See Manfioletti et al., *Mol. Cell. Biol.* 13(8):4976-4985 (1993) and Stitt et al., *Cell* 80:661-670 (1995). Manfioletti et al. (1993), *supra*, have suggested that the gas6 protein is member of the vitamin K-dependent family of proteins, wherein the members of the latter family of proteins (which include, for example, Protein S, Protein C and Factor X) all play regulatory roles in the blood coagulation pathway. Thus, it has been suggested that gas6 may play a role in the regulation of a protease cascade relevant in growth regulation or in the blood coagulation cascade.

Given the physiological importance of the gas6 protein, efforts are currently being undertaken by both industry and academia to identify new, native proteins which are homologous to gas6. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins, specifically those having homology to gas6. Examples of such screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. We herein describe the identification of a novel polypeptide which has homology to the gas6 polypeptide.

2. PRO274

The 7-transmembrane ("7TM") proteins or receptors, also referred to in the literature as G-protein coupled receptors, are specialized proteins designed for recognition of ligands and the subsequent signal transduction of information contained within those ligands to the machinery of the cell. The primary purpose of cell surface receptors is to discriminate appropriate ligands from the various extracellular stimuli which each cell encounters, then to activate an effector system that produces an intracellular signal, thereby controlling cellular processes. [Dohlman, H., Ann. Rev. Biochem., 60:653 (1991)]. The ability of 7TM receptors to bind ligand to a recognition domain and allosterically transmit the information to an intracellular domain is a

specialized feature of 7TM proteins [Kenakin, T., Pharmacol. Rev., 48:413 (1996)]. The gene family which encodes the 7TM receptors or G-protein linked receptors encode receptors which recognize a large number of ligands, including but not limited to, C5a, interleukin 8 and related chemokines. Research in this area suggests that distinct signals at the cell surface feed into common pathways of cell activation. [Gerard, C. and Gerard, N.,Curr. Op. Immunol., 6:140 (1994), Gerard, C. and Gerard, N.,Ann. Rev. Immunol., 12:775 (1994)]. The superfamily of 7TM or G-protein coupled receptors contains several hundred members able to recognize various messages such as photons, ions and amino acids among others [Schwartz, T.W., et al., H.,Trends in Pharmacol. Sci., 17(6):213 (1996)].

[Dohlman, H.,Ann. Rev. Biochem., 60:653 (1991)]. [Schwartz, T.W., et al., H.,Eur. J. Pharm. Sci., 2:85 (1994)]. We describe herein the identification of a novel polypeptide (designated herein as PRO274) which has homology to the 7 transmembrane segment receptor proteins and the Fn54 protein.

3. PRO300

The Diff 33 protein is over-expressed in mouse testicular tumors. At present its role is unclear, however, it may play a role in cancer. Given the medical importance of understanding the physiology of cancer, efforts are currently being under taken to identify new, native proteins which are involved in cancer. We describe herein the identification of a novel polypeptide which has homology to Diff 33, designated herein as PRO300.

4. PRO284

Efforts arre currently being undertaken to identify and characterize novel transmembrane proteins. We herein describe the identification and characterization of a novel transmembrane polypeptide, designated herein as PRO284.

5. PRO296

Cancerous cells often express numerous proteins that are not expressed in the corresponding normal cell type or are expressed at different levels than in the corresponding normal cell type. Many of these proteins are involved in inducing the transformation from a normal cell to a cancerous cell or in maintaining the cancer phenotype. As such, there is significant interest in identifying and characterizing proteins that are expressed in cancerous cells. We herein describe the identification and characterization of a novel polypeptide having homology to the sarcoma-amplified protein SAS, designated herein as PRO296.

6. PRO329

Immunoglobulin molecules play roles in many important mammalian physiological processes. The structure of immunoglobulin molecules has been extensively studied and it has been well documented that intact immunoglobulins possess distinct domains, one of which is the constant domain or F_c region of the immunoglobulin molecule. The F_c domain of an immunoglobulin, while not being directly involved in antigen

recognition and binding, does mediate the ability of the immunoglobulin molecule, either uncomplexed or complexed with its respective antigen, to bind to F_c receptors either circulating in the serum or on the surface of cells. The ability of an F_c domain of an immunoglobulin to bind to an F_c receptor molecule results in a variety of important activities, including for example, in mounting an immune response against unwanted foreign particles. As such, there is substantial interest in identifying novel F_c receptor proteins and subunits thereof. We herein describe the identification and characterization of a novel polypeptide having homology to a high affinity immunoglobulin F_c receptor protein, designated herein as PRO329.

7. **PRO362**

Colorectal carcinoma is a malignant neoplastic disease which has a high incidence in the Western world, particularly in the United States. Tumors of this type often metastasize through lymphatic and vascular channels and result in the death of some 62,000 persons in the United States annually.

Monoclonal antibody A33 (mAbA33) is a murine immunoglobulin that has undergone extensive preclinical analysis and localization studies in patients inflicted with colorectal carcinoma (Welt et al., *J. Clin. Oncol.* 8:1894-1906 (1990) and Welt et al., *J. Clin. Oncol.* 12:1561-1571 (1994)). mAbA33 has been shown to bind to an antigen found in and on the surface of normal colon cells and colon cancer cells. In carcinomas originating from the colonic mucosa, the A33 antigen is expressed homogeneously in more than 95% of the cases. The A33 antigen, however, has not been detecting in a wide range of other normal tissues, i.e., its expression appears to be rather organ specific. Therefore, the A33 antigen appears to play an important role in the induction of colorectal cancer.

Given the obvious importance of the A33 antigen in tumor cell formation and/or proliferation, there is substantial interest in identifying homologs of the A33 antigen. In this regard, we herein describe the identification and characterization of a novel polypeptide having homology to the A33 antigen protein, designated herein as PRO362.

8. **PRO363**

The cell surface protein HCAR is a membrane-bound protein that acts as a receptor for subgroup C of the adenoviruses and subgroup B of the coxsackieviruses. Thus, HCAR may provide a means for mediating viral infection of cells in that the presence of the HCAR receptor on the cellular surface provides a binding site for viral particles, thereby facilitating viral infection.

In light of the physiological importance of membrane-bound proteins and spcficially those which serve a cell surface receptor for viruses, efforts are currently being undertaken by both industry and academia to identify new, native membrane-bound reeptor proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. We herein describe a novel membrane-bound polypeptide having homology to the cell surface protein HCAR and to various tumor antigens including A33 and carcinoembryonic antigen, designated herein as PRO363, wherein this

polypeptide may be a novel cell surface virus receptor or tumor antigen.

9. PRO868

Control of cell numbers in mammals is believed to be determined, in part, by a balance between cell proliferation and cell death. One form of cell death, sometimes referred to as necrotic cell death, is typically characterized as a pathologic form of cell death resulting from some trauma or cellular injury. In contrast, there is another, "physiologic" form of cell death which usually proceeds in an orderly or controlled manner. This orderly or controlled form of cell death is often referred to as "apoptosis" [see, *e.g.*, Barr et al., Bio/Technology, 12:487-493 (1994); Steller et al., Science, 267:1445-1449 (1995)]. Apoptotic cell death naturally occurs in many physiological processes, including embryonic development and clonal selection in the immune system [Itoh et al., Cell, 66:233-243 (1991)]. Decreased levels of apoptotic cell death have been associated with a variety of pathological conditions, including cancer, lupus, and herpes virus infection [Thompson, Science, 267:1456-1462 (1995)]. Increased levels of apoptotic cell death may be associated with a variety of other pathological conditions, including AIDS, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, retinitis pigmentosa, cerebellar degeneration, aplastic anemia, myocardial infarction, stroke, reperfusion injury, and toxin-induced liver disease [see, Thompson, supra].

Apoptotic cell death is typically accompanied by one or more characteristic morphological and biochemical changes in cells, such as condensation of cytoplasm, loss of plasma membrane microvilli, segmentation of the nucleus, degradation of chromosomal DNA or loss of mitochondrial function. A variety of extrinsic and intrinsic signals are believed to trigger or induce such morphological and biochemical cellular changes [Raff, Nature, 356:397-400 (1992); Steller, supra; Sachs et al., Blood, 82:15 (1993)]. For instance, they can be triggered by hormonal stimuli, such as glucocorticoid hormones for immature thymocytes, as well as withdrawal of certain growth factors [Watanabe-Fukunaga et al., Nature, 356:314-317 (1992)]. Also, some identified oncogenes such as *myc*, *rel*, and *EIA*, and tumor suppressors, like *p53*, have been reported to have a role in inducing apoptosis. Certain chemotherapy drugs and some forms of radiation have likewise been observed to have apoptosis-inducing activity [Thompson, supra].

Various molecules, such as tumor necrosis factor-α ("TNF-α"), tumor necrosis factor-β ("TNF-β" or "lymphotoxin-α"), lymphotoxin-β ("LT-β"), CD30 ligand, CD27 ligand, CD40 ligand, OX-40 ligand, 4-1BB ligand, Apo-1 ligand (also referred to as Fas ligand or CD95 ligand), and Apo-2 ligand (also referred to as TRAIL) have been identified as members of the tumor necrosis factor ("TNF") family of cytokines [See, e.g., Gruss and Dower, Blood, 85:3378-3404 (1995); Pitti et al., J. Biol. Chem., 271:12687-12690 (1996); Wiley et al., Immunity, 3:673-682 (1995); Browning et al., Cell, 72:847-856 (1993); Armitage et al. Nature, 357:80-82 (1992), WO 97/01633 published January 16, 1997; WO 97/25428 published July 17, 1997]. Among these molecules, TNF-α, TNF-β, CD30 ligand, 4-1BB ligand, Apo-1 ligand, and Apo-2 ligand (TRAIL) have been reported to be involved in apoptotic cell death. Both TNF-α and TNF-β have been reported to induce apoptotic death in susceptible tumor cells [Schmid et al., Proc. Natl. Acad. Sci., 83:1881 (1986); Dealtry et al., Eur. J.

Immunol., 17:689 (1987)]. Zheng et al. have reported that TNF-α is involved in post-stimulation apoptosis of CD8-positive T cells [Zheng et al., Nature, 377:348-351 (1995)]. Other investigators have reported that CD30 ligand may be involved in deletion of self-reactive T cells in the thymus [Amakawa et al., Cold Spring Harbor Laboratory Symposium on Programmed Cell Death, Abstr. No. 10, (1995)].

Mutations in the mouse Fas/Apo-1 receptor or ligand genes (called *lpr* and *gld*, respectively) have been associated with some autoimmune disorders, indicating that Apo-1 ligand may play a role in regulating the clonal deletion of self-reactive lymphocytes in the periphery [Krammer et al., Curr. Op. Immunol., 6:279-289 (1994); Nagata et al., Science, 267:1449-1456 (1995)]. Apo-1 ligand is also reported to induce post-stimulation apoptosis in CD4-positive T lymphocytes and in B lymphocytes, and may be involved in the elimination of activated lymphocytes when their function is no longer needed [Krammer et al., supra; Nagata et al., supra]. Agonist mouse monoclonal antibodies specifically binding to the Apo-1 receptor have been reported to exhibit cell killing activity that is comparable to or similar to that of TNF-α [Yonehara et al., J. Exp. Med., 169:1747-1756 (1989)].

Induction of various cellular responses mediated by such TNF family cytokines is believed to be initiated by their binding to specific cell receptors. Two distinct TNF receptors of approximately 55-kDa (TNFR1) and 75-kDa (TNFR2) have been identified [Hohman et al., J. Biol. Chem., 264:14927-14934 (1989); Brockhaus et al., Proc. Natl. Acad. Sci., 87:3127-3131 (1990); EP 417,563, published March 20, 1991] and human and mouse cDNAs corresponding to both receptor types have been isolated and characterized [Loetscher et al., Cell, 61:351 (1990); Schall et al., Cell, 61:361 (1990); Smith et al., Science, 248:1019-1023 (1990); Lewis et al., Proc. Natl. Acad. Sci., 88:2830-2834 (1991); Goodwin et al., Mol. Cell. Biol., 11:3020-3026 (1991)]. Extensive polymorphisms have been associated with both TNF receptor genes [see, e.g., Takao et al., Immunogenetics, 37:199-203 (1993)]. Both TNFRs share the typical structure of cell surface receptors including extracellular, transmembrane and intracellular regions. The extracellular portions of both receptors are found naturally also as soluble TNF-binding proteins [Nophar, Y. et al., EMBO J., 9:3269 (1990); and Kohno, T. et al., Proc. Natl. Acad. Sci. U.S.A., 87:8331 (1990)]. More recently, the cloning of recombinant soluble TNF receptors was reported by Hale et al. [J. Cell. Biochem. Supplement 15F, 1991, p. 113 (P424)].

The extracellular portion of type 1 and type 2 TNFRs (TNFR1 and TNFR2) contains a repetitive amino acid sequence pattern of four cysteine-rich domains (CRDs) designated 1 through 4, starting from the NH_2-terminus. Each CRD is about 40 amino acids long and contains 4 to 6 cysteine residues at positions which are well conserved [Schall et al., supra; Loetscher et al., supra; Smith et al., supra; Nophar et al., supra; Kohno et al., supra]. In TNFR1, the approximate boundaries of the four CRDs are as follows: CRD1- amino acids 14 to about 53; CRD2- amino acids from about 54 to about 97; CRD3- amino acids from about 98 to about 138; CRD4- amino acids from about 139 to about 167. In TNFR2, CRD1 includes amino acids 17 to about 54; CRD2- amino acids from about 55 to about 97; CRD3- amino acids from about 98 to about 140; and CRD4- amino acids from about 141 to about 179 [Banner et al., Cell, 73:431-435 (1993)]. The potential role of the CRDs in ligand binding is also described by Banner et al., supra.

A similar repetitive pattern of CRDs exists in several other cell-surface proteins, including the p75 nerve

growth factor receptor (NGFR) [Johnson et al., Cell, 47:545 (1986); Radeke et al., Nature, 325:593 (1987)], the B cell antigen CD40 [Stamenkovic et al., EMBO J., 8:1403 (1989)], the T cell antigen OX40 [Mallet et al., EMBO J., 9:1063 (1990)] and the Fas antigen [Yonehara et al., supra and Itoh et al., Cell, 66:233-243 (1991)]. CRDs are also found in the soluble TNFR (sTNFR)-like T2 proteins of the Shope and myxoma poxviruses [Upton et al., Virology, 160:20-29 (1987); Smith et al., Biochem. Biophys. Res. Commun., 176:335 (1991); Upton et al., Virology, 184:370 (1991)]. Optimal alignment of these sequences indicates that the positions of the cysteine residues are well conserved. These receptors are sometimes collectively referred to as members of the TNF/NGF receptor superfamily. Recent studies on p75NGFR showed that the deletion of CRD1 [Welcher, A.A. et al., Proc. Natl. Acad. Sci. USA, 88:159-163 (1991)] or a 5-amino acid insertion in this domain [Yan, H. and Chao, M.V., J. Biol. Chem., 266:12099-12104 (1991)] had little or no effect on NGF binding [Yan, H. and Chao, M.V., supra]. p75 NGFR contains a proline-rich stretch of about 60 amino acids, between its CRD4 and transmembrane region, which is not involved in NGF binding [Peetre, C. et al., Eur. J. Hematol., 41:414-419 (1988); Seckinger, P. et al., J. Biol. Chem., 264:11966-11973 (1989); Yan, H. and Chao, M.V., supra]. A similar proline-rich region is found in TNFR2 but not in TNFR1.

The TNF family ligands identified to date, with the exception of lymphotoxin-α, are type II transmembrane proteins, whose C-terminus is extracellular. In contrast, most receptors in the TNF receptor (TNFR) family identified to date are type I transmembrane proteins. In both the TNF ligand and receptor families, however, homology identified between family members has been found mainly in the extracellular domain ("ECD"). Several of the TNF family cytokines, including TNF-α, Apo-1 ligand and CD40 ligand, are cleaved proteolytically at the cell surface; the resulting protein in each case typically forms a homotrimeric molecule that functions as a soluble cytokine. TNF receptor family proteins are also usually cleaved proteolytically to release soluble receptor ECDs that can function as inhibitors of the cognate cytokines.

Recently, other members of the TNFR family have been identified. Such newly identified members of the TNFR family include CAR1, HVEM and osteoprotegerin (OPG) [Brojatsch et al., Cell, 87:845-855 (1996); Montgomery et al., Cell, 87:427-436 (1996); Marsters et al., J. Biol. Chem., 272:14029-14032 (1997); Simonet et al., Cell, 89:309-319 (1997)]. Unlike other known TNFR-like molecules, Simonet et al., supra, report that OPG contains no hydrophobic transmembrane-spanning sequence.

Moreover, a new member of the TNF/NGF receptor family has been identified in mouse, a receptor referred to as "GITR" for "glucocorticoid-induced tumor necrosis factor receptor family-related gene" [Nocentini et al., Proc. Natl. Acad. Sci. USA 94:6216-6221 (1997)]. The mouse GITR receptor is a 228 amino acid type I transmembrane protein that is expressed in normal mouse T lymphocytes from thymus, spleen and lymph nodes. Expression of the mouse GITR receptor was induced in T lymphocytes upon activation with anti-CD3 antibodies, Con A or phorbol 12-myristate 13-acetate. It was speculated by the authors that the mouse GITR receptor was involved in the regulation of T cell receptor-mediated cell death.

In Marsters et al., Curr. Biol., 6:750 (1996), investigators describe a full length native sequence human polypeptide, called Apo-3, which exhibits similarity to the TNFR family in its extracellular cysteine-rich repeats and resembles TNFR1 and CD95 in that it contains a cytoplasmic death domain sequence [see also Marsters et

al., Curr. Biol., 6:1669 (1996)]. Apo-3 has also been referred to by other investigators as DR3, wsl-1 and TRAMP [Chinnaiyan et al., Science, 274:990 (1996); Kitson et al., Nature, 384:372 (1996); Bodmer et al., Immunity, 6:79 (1997)].

Pan et al. have disclosed another TNF receptor family member referred to as "DR4" [Pan et al., Science, 276:111-113 (1997)]. The DR4 was reported to contain a cytoplasmic death domain capable of engaging the cell suicide apparatus. Pan et al. disclose that DR4 is believed to be a receptor for the ligand known as Apo-2 ligand or TRAIL.

In Sheridan et al., Science, 277:818-821 (1997) and Pan et al., Science, 277:815-818 (1997), another molecule believed to be a receptor for the Apo-2 ligand (TRAIL) is described. That molecule is referred to as DR5 (it has also been alternatively referred to as Apo-2). Like DR4, DR5 is reported to contain a cytoplasmic death domain and be capable of signaling apoptosis.

In Sheridan et al., supra, a receptor called DcR1 (or alternatively, Apo-2DcR) is disclosed as being a potential decoy receptor for Apo-2 ligand (TRAIL). Sheridan et al. report that DcR1 can inhibit Apo-2 ligand function *in vitro*. See also, Pan et al., supra, for disclosure on the decoy receptor referred to as TRID.

For a review of the TNF family of cytokines and their receptors, see Gruss and Dower, supra.

As presently understood, the cell death program contains at least three important elements - activators, inhibitors, and effectors; in *C. elegans*, these elements are encoded respectively by three genes, *Ced-4*, *Ced-9* and *Ced-3* [Steller, Science, 267:1445 (1995); Chinnaiyan et al., Science, 275:1122-1126 (1997); Wang et al., Cell, 90:1-20 (1997)]. Two of the TNFR family members, TNFR1 and Fas/Apo1 (CD95), can activate apoptotic cell death [Chinnaiyan and Dixit, Current Biology, 6:555-562 (1996); Fraser and Evan, Cell; 85:781-784 (1996)]. TNFR1 is also known to mediate activation of the transcription factor, NF-κB [Tartaglia et al., Cell, 74:845-853 (1993); Hsu et al., Cell, 84:299-308 (1996)]. In addition to some ECD homology, these two receptors share homology in their intracellular domain (ICD) in an oligomerization interface known as the death domain [Tartaglia et al., supra; Nagata, Cell, 88:355 (1997)]. Death domains are also found in several metazoan proteins that regulate apoptosis, namely, the Drosophila protein, Reaper, and the mammalian proteins referred to as FADD/MORT1, TRADD, and RIP [Cleaveland and Ihle, Cell, 81:479-482 (1995)].

Upon ligand binding and receptor clustering, TNFR1 and CD95 are believed to recruit FADD into a death-inducing signalling complex. CD95 purportedly binds FADD directly, while TNFR1 binds FADD indirectly via TRADD [Chinnaiyan et al., Cell, 81:505-512 (1995); Boldin et al., J. Biol. Chem., 270:387-391 (1995); Hsu et al., supra; Chinnaiyan et al., J. Biol. Chem., 271:4961-4965 (1996)]. It has been reported that FADD serves as an adaptor protein which recruits the *Ced-3*-related protease, MACHα/FLICE (caspase 8), into the death signalling complex [Boldin et al., Cell, 85:803-815 (1996); Muzio et al., Cell, 85:817-827 (1996)]. MACHα/FLICE appears to be the trigger that sets off a cascade of apoptotic proteases, including the interleukin-1β converting enzyme (ICE) and CPP32/Yama, which may execute some critical aspects of the cell death programme [Fraser and Evan, supra].

It was recently disclosed that programmed cell death involves the activity of members of a family of cysteine proteases related to the *C. elegans* cell death gene, *ced-3*, and to the mammalian IL-1-converting

enzyme, ICE. The activity of the ICE and CPP32/Yama proteases can be inhibited by the product of the cowpox virus gene, *crmA* [Ray et al., Cell, 69:597-604 (1992); Tewari et al., Cell, 81:801-809 (1995)]. Recent studies show that CrmA can inhibit TNFR1- and CD95-induced cell death [Enari et al., Nature, 375:78-81 (1995); Tewari et al., J. Biol. Chem., 270:3255-3260 (1995)].

As reviewed recently by Tewari et al., TNFR1, TNFR2 and CD40 modulate the expression of proinflammatory and costimulatory cytokines, cytokine receptors, and cell adhesion molecules through activation of the transcription factor, NF-κB [Tewari et al., Curr. Op. Genet. Develop., 6:39-44 (1996)]. NF-κB is the prototype of a family of dimeric transcription factors whose subunits contain conserved Rel regions [Verma et al., Genes Develop., 9:2723-2735 (1996); Baldwin, Ann. Rev. Immunol., 14:649-681 (1996)]. In its latent form, NF-κB is complexed with members of the IκB inhibitor family; upon inactivation of the IκB in response to certain stimuli, released NF-κB translocates to the nucleus where it binds to specific DNA sequences and activates gene transcription.

10. PRO382

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized, including the serine proteases which exhibit specific activity toward various serine-containing proteins. The mammalian protease enzymes play important roles in biological processes such as, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

In light of the important physiological roles played by protease enzymes, efforts are currently being undertaken by both industry and academia to identify new, native protease homologs. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. We herein describe the identification of novel polypeptides having homology to serine protease enzymes, designated herein as PRO382 polypeptides.

11. PRO545

The ADAM (A Disintegrin And Metalloprotease) family of proteins of which meltrin is a member may have an important role in cell interactions and in modulating cellular responses. [see, for example, Gilpin et al., J. Biol. Chem., 273(1):157-166 (1998)]. The ADAM proteins have been implicated in carcinogenesis. Meltrin-α (ADAM12) is a myoblast gene product reported to be required for cell fusion. [Harris et al., J. Cell. Biochem., 67(1):136-142 (1997), Yagami-Hiromasa et al., Nature, 377:652-656 (1995)]. The meltrins contain disintegrin and metalloprotease domains and are implicated in cell adhesive events involved in development, through the integrin-binding disintegrin domain, but also have an anti-adhesive function through a zinc-dependent metalloprotease domain. [Alfandari et al., Devel. Biol., 182(2):314-330 (1997)]. Given the medical importance

of cell fusion and modulation of cellular responses in carcinogenesis and other disease mechanisms, efforts are currently being under taken to identify new, native proteins which are involved in cell fusion and modulation of cellular responses. We describe herein the identification of a novel polypeptide which has homology to meltrin, designated herein as PRO545.

12. PRO617

CD24 is a protein that is associated with the cell surface of a variety of different cells of the mammalian immune system, including for example, neutrophils, monocytes and some lymphocytes, for example, B lymphocytes. CD24 has been shown to be a ligand for the platelet-associated surface glycoprotein P-selectin (also known as granule membrane protein-140 or GMP-140), a glycoprotein that is constitutively synthesized in both platelets and endothelial cells and becomes exposed on the surface of platelets when those cells become activated. In this way, P-selectin mediates the calcium-dependent adhesion of activated platelets and endothelial cells to the various cells of the immune system that express one or more ligands for the P-selectin molecule, particularly CD24. This mechanism allows for recruitment of immune system cells to locations where they are most needed, for example, sites of injury. Thus, there is substantial interest in identifying novel polypeptides that exhibit homology to the cell surface antigens of the immune system cells. We herein describe the identification and characterization of a novel polypeptide having homology to the CD24 protein, wherein that novel polypeptide is herein designated PRO617.

13. PRO700

Protein-disulfide isomerase (PDI) is a catalyst of disulfide formation and isomerization during protein folding. It has two catalytic sites housed in two domains homologous to thioredoxin, one near the N terminus and the other near the C terminus. [See for example, Gilbert HF, J.Biol.Chem., 47:29399-29402 (1997), Mayfield KJ, Science, 278:1954-1957 (1997) and Puig et al., J.Biol.Chem., 52:32988-32994 (1997)]. PDI is useful for formation of natural type disulfide bonds in a protein which is produced in aprokaryotic cell. (See also, U.S. Patent Nos. 5,700,659 and 5,700,678).

Thus, PDI and molecules related thereto are of interest, particularly for ability to catalyze the formation of disulfide bonds. Moreover, these molecules are generally of interest in the study of redox reactions and related processes. PDI and related molecules are further described in Darby, et al., Biochemistry 34, 11725-11735 (1995). We herein describe the identification and characterization of novel polypeptides having homology to protein disulfide isomerase, designated herein as PRO700 polypeptides.

14. PRO702

Conglutinin is a bovine serum protein that was originally described as a vertebrate lectin protein and which belongs to the family of C-type lectins that have four characteristic domains, (1) an N-terminal cysteine-rich domain, (2) a collagen-like domain, (3) a neck domain and (4) a carbohydrate recognition domain (CRD). Recent reports have demonstrated that bovine conglutinin can inhibit hemagglutination by influenza A viruses

as a result of their lectin properties (Eda et al., Biochem. J. 316:43-48 (1996)). It has also been suggested that lectins such as conglutinin can function as immunoglobulin-independent defense molecules due to complement-mediated mechanisms. Thus, conglutinin has been shown to be useful for purifying immune complexes *in vitro* and for removing circulating immune complexes from patients plasma *in vivo* (Lim et al., Biochem. Biophys. Res. Commun. 218:260-266 (1996)). We herein describe the identification and characterization of a novel polypeptide having homology to the conglutinin protein, designated herein as PRO702.

15. PRO703

Very-long-chain acyl-CoA synthetase ("VLCAS") is a long-chain fatty acid transport protein which is active in the cellular transport of long and very long chain fatty acids. [see for example, Uchida et al., J Biochem (Tokyo) 119(3):565-571 (1996) and Uchiyama et al., J Biol Chem 271(48):30360-30365 (1996). Given the biological importance of fatty acid transport mechanisms, efforts are currently being under taken to identify new, native proteins which are involved in fatty acid transport. We describe herein the identification of a novel polypeptide which has homology to VLCAS, designated herein as PRO703.

16. PRO705

The glypicans are a family of glycosylphosphatidylinositol (GPI)-anchored proteoglycans that, by virtue of their cell surface localization and possession of heparin sulfate chains, may regulate the responses of cells to numerous heparin-binding growth factors, cell adhesion molecules and extracellular matrix components. Mutations in one glypican protein cause of syndrome of human birth defects, suggesting that the glypicans may play an important role in development (Litwack et al., Dev. Dyn. 211:72-87 (1998)). Also, since the glypicans may interact with the various extracellular matrices, they may also play important roles in wound healing (McGrath et al., Pathol. 183:251-252 (1997)). Furthermore, since glypicans are expressed in neurons and glioma cells, they may also play an important role in the regulation of cell division and survival of cells of the nervous system (Liang et al., J. Cell. Biol. 139:851-864 (1997)). It is evident, therefore, that the glypicans are an extremely important family of proteoglycans. There is, therefore, substantial interest in identifying novel polypeptides having homology to members of the glypican family. We herein describe the identification and characterization of a novel polypeptide having homology to K-glypican, designated herein as PRO705.

17. PRO708

Aryl sulfatases are enzymes that exist in a number of different isoforms, including aryl sulfatase A (ASA), aryl sulfatase B (ASB) and aryl sulfatase C (ASC), and that function to hydrolyze a variety of different aromatic sulfates. Aryl sulfatases have been isolated from a variety of different animal tissues and microbial sources and their structures and functions have been extensively studied (see, e.g., Nichol and Roy, J. Biochem. 55:643-651 (1964)). ASA deficiency has been reported to be associated with metachromatic leukodystrophy (MLD) (Giles et al., Prenat. Diagn. 7(4):245-252 (1987) and Herska et al., Am. J. Med. Genet. 26(3):629-635 (1987)). Additionally, other groups have reported that aryl sulfatases have been found in high levels in natural

killer cells of the immune system and have hypothesized a possible role for these enzymes in NK cell-mediated cellular lysis (see, e.g., Zucker-Franklin et al., Proc. Natl. Acad. Sci. USA 80(22):6977-6981 (1983)). Given the obvious physiological importance of the aryl sulfatase enzymes, there is a substantial interest in identifying novel aryl sulfatase homolog polypeptides. We herein describe the identification and characterization of novel polypeptides having homology to the aryl sulfatases, wherein these novel polypeptides are herein designated PRO708 polypeptides.

18. PRO320

Fibulin-1 is a cysteine-rich, calcium-binding extracellular matrix (ECM) component of basement membranes and connective tissue elastic fibers and plasma protein, which has four isoforms, A-D, derived from alternative splicing. Fibulin-1 is a modular glycoprotein with amino-terminal anaphlatoxin-likemodules followed by nine epidermal growth factor (EGF)-like modules and, depending on alternative splicing, four possible carboxyl termini. Fibulin-2 is a novel extracellular matrix protein frequently found in close association with microfibrils containing either fibronectin or fibrillin. There are multiple forms of fibulin-1 that differ in their C-terminal regions that are produced through the process of alternative splicing of their precursor RNA. [see for example Tran et al., Matrix Biol 15(7):479-493 (1997).]

Northern and Western blotting analysis of 16 cell lines established from tumors formed in athymic mice and malignant cell lines derived from patients indicate that low expression of fibulin-1D plays a role in tumor formation and invasion. [Qing et al., Oncogene, 18:2159-2168 (1997)]. Ovarian-cancer cells are characterized by their ability to invade freely the peritoneal cavity. It has been demonstrated that estradiol stimulates the proliferation of estrogen-receptor (ER)-positive ovarian-cancer cells, as well as expression of fibulin-1. Studies on the effect of fibulin-1 on motility of the MDA-MB231 breast-cancer cell line, indicated inhibition of haptotactic migration of MDA-MB231 cells, and the authors concluded that fibulin-1 can inhibit cancer cell motility *in vitro* and therefore has the potential to inhibit tumor invasion. [Hayashido et al., Int J Cancer , 75(4):654-658 (1998)]

Thus, fibulin, and molecules related thereto are of interest, particularly for the use of preventing cancer. Moreover, these molecules are generally of interest in the study of connective tissue and attachment molecules and related mechanisms. Fibulin and related molecules are further described in Adams, et al., J. Mol. Biol., 272(2):226-36 (1997); Kielty and Shuttleworth, Microsc. Res. Tech., 38(4):413-27 (1997); and Child, J. Card. Surg,. 12(2Supp.):131-5 (1997).

We herein describe the identification and characterization of novel polypeptides having homology to fibulin, designated herein as PRO320 polypeptides.

19. PRO324

Oxidoreductases are enzymes that catalyze a reaction in which two molecules of a compound interact so that one molecule is oxidized and the other is reduced, with a molecule of water entering the reaction. There are many different types of oxidoreductase enzymes that play very important physiological roles in the

mammalian organism. Some of the most important oxidoreductases include, for example, lyases, lactases, cholesterol oxidases, and the like. These enzymes play roles in such essential processes as digestion, signal transduction, maintenance of ionic homeostasis, and the like. As such, given that oxidoreductase enzymes find various essential uses in the mammalian organism, there is a substantial interest in identifying novel oxidoreductase enzyme homologs. We herein describe the identification and characterization of a novel polypeptide having homology to oxidoreductases, designated herein as PRO324.

20. PRO351

Prostasin is a novel human serine proteinase purified from human seminal fluid. Immunohistochemical localization reveals that prostasin is present in epithelial cells and ducts of the prostate gland. The cDNA for prostasin has been cloned and characterized. Southern blot analysis, following a reverse transcription polymerase chain reaction, indicates that prostasin mRNA is expressed in prostate, liver, salivary gland, kidney, lung, pancreas, colon, bronchus, renal proximal tubular cells, and prostate carcinoma LNCaP cells. Cellular localization of prostasin mRNA was identified within epithelial cells of the human prostate gland by in situ hybridization histochemistry. [See for example, Yu et al., J Biol Chem. (1994) 269(29):18843-18848, and Yu et al., J Biol Chem. (1994) 270(22):13483-13489].

Thus, prostasin, and molecules related thereto are of interest, particularly for the study, diagnosis and treatment of medical conditions involving the prostate. Prostasin and related molecules are further described in Yu et al., Genomics (1996) 32(3):334-340. We herein describe the identification and characterization of novel polypeptides having homology to prostasin, designated herein as PRO351 polypeptides.

21. PRO352

Butyrophilin is a milk glycoprotein that constitutes more than 40% of the total protein associated with the fat globule membrane in mammalian milk. Expression of butyrophilin mRNA has been shown to correlate with the onset of milk fat production toward the end pregnancy and is maintained throughout lactation. Butyrophilin has been identified in bovine, murine and human (see Taylor et al., Biochim. Biophys. Acta 1306:1-4 (1996), Ishii et al., Biochim. Biophys. Acta 1245:285-292 (1995), Mather et al., J. Dairy Sci. 76:3832-3850 (1993) and Banghart et al., J. Biol. Chem. 273:4171-4179 (1998)) and is a type I transmembrane protein that is incorporated into the fat globulin membrane. It has been suggested that butyrophilin may play a role as the principle scaffold for the assembly of a complex with xanthine dehydrogenase/oxidase and other proteins that function in the budding and release of milk-fat globules from the apical surface during lactation (Banghart et al., supra).

Given that butyrophilin plays an obviously important role in mammalian milk production, there is substantial interest in identifying novel butyrophilin homologs. We herein describe the identification and characterization of a novel polypeptide having homology to butyrophilin, designated herein as PRO352.

22. PRO381

The immunophilins are a family of proteins that function as receptors for immunosuppressant drugs, such as cyclosporin A, FK506, and rapamycin. The immunophilins occur in two separate classes, (1) the FK506-binding proteins (FKBPs), which bind to FK506 and rapamycin, and (2) the cyclophilins, which bind to cyclosporin A. With regard to the FK506-binding proteins, it has been reported that the FK506/FKBP complex functions to inhibit the activity of the serine/threonine protein phosphatase 2B (calcineurin), thereby providing immunosuppressant activity (Gold, Mol. Neurobiol. 15:285-306 (1997)). It has also been reported that the FKBP immunophilins are found in the mammalian nervous system and may be involved in axonal regeneration in the central nervous system through a mechanism that is independent of the process by which immunosuppression is achieved (Gold, *supra*). Thus, there is substantial interest in identifying novel polypeptides having homology to the FKBP immunophilins. We herein describe the identification and characterization of a novel polypeptide having homology to an FKBP immunophilin protein, designated herein as PRO381.

23. PRO386

Mammalian cell membranes perform very important functions relating to the structural integrity and activity of various cells and tissues. Of particular interest in membrane physiology is the study of transmembrane ion channels which act to directly control a variety of physiological, pharmacological and cellular processes. Numerous ion channels have been identified including calcium (Ca), sodium (Na) and potassium (K) channels, each of which have been analyzed in detail to determine their roles in physiological processes in vertebrate and insect cells.

One type of cell membrane-associated ion channel, the sodium channel, plays an extremely important role in a cell's ability to maintain ionic homeostasis as well as transmit intracellular and extracellular signals. Voltage-gated sodium channels in brain neurons have been shown to be complexes of a pore-forming alpha unit with smaller beta-1 and beta-2 subunits (Isom et al., Cell 83:433-442 (1995)). Given the obvious importance of sodium channels in cellular homeostasis and other important physiological functions, there is a significant interest in identifying novel polypeptides having homology to sodium channel subunits. We herein describe the identification and characterization of a novel polypeptide having homology to the beta-2 subunit of the rat sodium channel, designated herein as PRO386.

24. PRO540

Lecithin-cholesterolacyltransferase("LCAT"), also known as phosphatidylcholine-sterol acyltransferase is a key enzyme in the intravascular metabolism of high density lipoproteins, specifically in the process of cholesterol metabolism. [see, for example, Brousseau et al., J. Lipid Res., 38(12):2537-2547 (1997), Hill et al., Biochem. J., 294:879-884 (1993), and Drayna et al., Nature 327 (6123):632-634 (1987)]. Given the medical importance of lipid metabolism, efforts are currently being under taken to identify new, native proteins which are involved in lipid transport. We describe herein the identification of a novel polypeptide which has homology

to LCAT, designated herein as PRO540.

25. PRO615

Synaptogyrin is a synaptic vesicle protein that is uniformly distributed in the nervous system. The cDNA encoding synaptogyrin has been cloned and sequenced and the sequence predicts a protein with a molecular mass of 25,900 D with four membrane-spanning domains. Synaptogyrin has been implicated in membrane traffic to and from the plasma membrane. Stenius et al., J. Cell. Biol. 131(6-2):1801-1809 (1995). In addition, a novel isoform of synaptogyrin called cellugyrin exhibits sequence identity with synaptogyrin. In rat tissues, cellugyrin and synaptogyrins are expressed in mirror image patterns. Cellugyrin is ubiquitously present in all tissues tested with the lowest levels in brain tissue, whereas synaptogyrin protein is only detectable in brain. In rat tissues, cellugyrin and synaptogyrins are expressed in mirror image patterns. The synaptic vesicle protein synaptogyrin may be a specialized version of a ubiquitous protein, cellugyrin, with the two proteins sharing structural similarity but differing in localization. This finding supports the emerging concept of synaptic vesicles as the simplified and specialized form of a generic trafficking organelle. [Janz et al., J. Biol. Chem. 273(5):2851-2857 (1998)] . The sequence for cellugyrin derived from the Norway rat, *Rattus norvegicus* has been deposited in the Genbank database on 23 December 1997, designated accession number AF039085. See also, Janz et al., J. Biol. Chem. 273 (1998), in press.

Given the medical importance of synaptic transmission, efforts are currently being under taken to identify new, native proteins that may be part of a simplified and specialized generic trafficking organelle in the form of synaptic vesicles. We describe herein the identification of a novel polypeptide which has homology to synaptogyrin, designated herein as PRO615.

26. PRO618

Enteropeptidase is a key enzyme in the intestinal digestion cascade specifically cleaves the acidic propeptide from trypsinogen to yield active trypsin. This cleavage initiates a cascade of proteolytic reactions leading to the activation of many pancreatic zymogens.
See, for example, Matsushima et al., J. Biol. Chem. 269(31):19976-19982 (1994), Kitamoto et al., Proc. Nat. Acad. Sci., 91(16):7588-7592 (1994). Enterokinase (enteropeptidase) is a related to mammalian serine proteases involved in digestion, coagulation, and fibrinolysis. LaVallie et al., J Biol Chem., 268(31):23311-23317 (1993).

Given the medical importance of digestive processes, efforts are currently being under taken to identify new, native proteins that may be involved in digestion, coagulation, and fibrinolysis. We describe herein the identification of a novel polypeptide which has homology to enteropeptidase, designated herein as PRO618.

27. PRO719

Lipoprotein lipase is a key enzyme that mediates the hydrolysis of triglycerides and phospholipids present in circulating plasma lipoproteins (Dugi et al., J. Biol. Chem.. 270:25396-25401 (1995)). Moreover, lipoprotein lipase has been shown to mediate the uptake of lipoproteins into cells, wherein cellular uptake of

lipoproteins is initiated by binding of lipoprotein lipase to cell surface proteoglycans and to the low density lipoprotein (LDL) receptor-related protein (Krapp et al., J. Lipid Res. 36:2362-2373 (1995)). Thus, it is clear that lipoprotein lipase plays an extremely important role in lipoprotein and cholesterol metabolism. There is, therefore, substantial interest in identifying novel polypeptides that share sequence homology and/or biological activity with lipoprotein lipase. We herein describe the identification and characterization of a novel polypeptide having sequence homology to lipoprotein lipase H, designated heein as PRO719.

28. PRO724

The low density lipoprotein (LDL) receptor is a membrane-bound protein that plays a key role in cholesterol homeostasis, mediating cellular uptake of lipoprotein particles by high affinity binding to its ligands, apolipoprotein (apo) B-100 and apoE. The ligand-binding domain of the LDL receptor contains 7 cysteine-rich repeats of approximately 40 amino acids, wherein each repeat contains 6 cysteines, which form 3 intra-repeat disulfide bonds. These unique structural features provide the LDL receptor with its ability to specifically interact with apo B-100 and apoE, thereby allowing for transport of these lipoprotein particles across cellular membranes and metabolism of their components. Soluble fragments containing the extracellular domain of the LDL receptor have been shown to retain the ability to interact with its specific lipoprotein ligands (Simmons et al., J. Biol. Chem. 272:25531-25536 (1997)). Thus, it is clear that the LDL receptor is intimately involved in important physiological activities related to cholesterol metabolism. As such, there is substantial interest in identifying novel LDL receptor homolog proteins. We herein describe the identification and characterization of a novel polypeptide having homology to the human LDL receptor protein, designated herein as PRO724..

29. PRO772

Expression of the human gene A4 is enriched in the colonic epithelium and is transcriptionally activated on differentiation of colonic epithelial cells in vitro (Oliva et al., Arch. Biochem. Biophys. 302:183-192 (1993) and Oliva et al., Am. J. Physiol. 272:C957-C965 (1997)). A4 cDNA contains an open reading frame that predicts a polypeptide of approximately 17 kilodaltons in size. Hydropathy analysis of the A4 protein revealed four putative membrane-spanning alpha-helices. Immunocytochemical studies of cells expressing A4 protein indicated that expression is localized to the endoplasmic reticulum. The four membrane-spanning domains and the biophysical characteristics of the A4 protein suggest that it belongs to a family of integral membrane proteins called proteolipids, some of which multimerize to form ion channels. In fact, preliminary evidence has suggested that A4 may itself multimerize and take on the properties of an ion channel (Oliva et al., Am. J. Physiol. 272:C957-C965 (1997)). Given the importance of ion channels in maintaining cellular homeostasis, there is a significant interest in identifying novel polypeptides having homology to known and putative ion channels. We herein describe the identification and characterization of a novel polypeptide having homology to the putative ion channel protein, A4, designated herein as PRO772.

30. PRO852

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized. The mammalian protease enzymes play important roles in many different biological processes including, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

In light of the important physiological roles played by protease enzymes, efforts are currently being undertaken by both industry and academia to identify new, native protease homologs. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. We herein describe the identification of novel polypeptides having homology to various protease enzymes, designated herein as PRO852 polypeptides.

31. PRO853

Studies have reported that the redox state of the cell is an important determinant of the fate of the cell. Furthermore, reactive oxygen species have been reported to be cytotoxic, causing inflammatory disease, including tissue necrosis, organ failure, atherosclerosis, infertility, birth defects, premature aging, mutations and malignancy. Thus, the control of oxidation and reduction is important for a number of reasons, including the control and prevention of strokes, heart attacks, oxidative stress, hypertension and may be associated with the development of malignancies. The levels of antioxidant enzymes, such as reductases, which catalyze the conversion of reactive oxygen species to water have been shown to be low in cancer cells. In particular, malignant prostate epithelium may have lowered expression of such antioxidant enzymes [Baker et ., Prostate 32(4):229-233 (1997)]. In this regard, reductases, are of interest. In addition, the transcription factors, NF-kappa B and AP-1, are known to be regulated by redox state and to affect the expression of a large variety of genes thought to be involved in the pathogenesis of AIDS, cancer, atherosclerosis and diabetic complications. Publications further describing this subject matter include Engman et al., Anticancer Res. (Greece), 17:4599-4605 (1997), Kelsey, et al., Br. J. Cancer, 76(7):852-4 (1997); Friedrich and Weiss, J. Theor. Biol., 187(4):529-40 (1997) and Pieulle, et al., J. Bacteriol., 179(18):5684-92 (1997). Given the physiological importance of redox reactions *in vivo*, efforts are currently being under taken to identify new, native proteins which are involved in redox reactions. We describe herein the identification of a novel prostate specific polypeptide which has sequence similarity to reductase, designated herein as PRO853.

32. PRO860

Neurofascin is a member of the L1 subgroup of the cellular adhesion molecule ("CAM") family of nervous system adhesion molecules and is involved in cellular aggregation. Cell-cell recognition and patterning

of cell contacts have a critical role in mediating reversible assembly of a wide variety or transcellular complexes in the nervous system. Cell interactions may be regulated through modulation of ankyrin binding to neurofascin. See, for example, Tuvia et al., Proc. Nat Acad. Sci., 94(24) 12957-12962 (1997). Neurofascin has been described as a member of the L1 subgroup of the immunoglobulin superfamily implicated in neurite extension during embryonic development for which numerous isoforms have been detected at various stages of development. See also Hassel et al., J. Biol. Chem., 272(45) 28742-28749 (1997), Grumet., Cell. Tissue Res. 290(2) 423-428 (1997), Garver et al., J. Cell. Biol., 137:703-714 (1997), and Lambert et al., J. Neurosci., 17:7025-7-36 (1997),.

Given the physiological importance of cellular adhesion molecules and development of the nervous system *in vivo*, efforts are currently being under taken to identify new, native proteins which are involved in regulation of cellular interactions in the nervous system. We describe herein the identification and characterization of a novel polypeptide which has sequence similarity to neurofascin, designated herein as PRO860.

33. PRO846

The CMRF35 monoclonal antibody was used to identify a cell membrane antigen, designated CMRF35, which is present on the surface of monocytes, neutrophils, a proportion of peripheral blood T and B lymphocytes and lymphocytic cell lines. The CMRF35 cDNA encodes a novel integral membrane glycoprotein member of the immunoglobulin (Ig) gene superfamily. The molecule comprises (a) a single extracellular Ig variable domain remarkably similar to the Fc receptor for polymeric IgA and IgM, (b) a membrane-proximal domain containing a high proportion of proline, serine and threonine residues that was predicted to be heavily O-glycosylated, (c) an unusual transmembrane anchor that contained a glutamic acid and a proline residue and (d) a short cytoplasmic tail. Transcripts encoding the CMRF35 protein have been detected in early monocytic cell lines, in peripheral blood T cells and in some B lymphoblastoid cell lines, confirming the results of immunocytological staining. Jackson et al., Eur. J. Immunol. 22(5):1157-1163 (1992). CMRF-35 molecules are differentially expressed in hematopoietic cells, and the expression of the antigen was shown to be markedly influenced by stimulation with mitogens and cytokines. See, for example, Clark et al., Exp. Hematol. 25(8):759 (1997), Daish et al., Immunol. 79(1):55-63 (1993), and Clark et al., Tissue Antigens 48:461 (1996).

Given the physiological importance of the immune system and antigens associated with various immune system cells, efforts are currently being under taken to identify new, native proteins which are expressed on various cells of the immune system. We describe herein the identification of a novel polypeptide which has sequence similarity to CMRF35, designated herein as PRO846.

34. PRO862

Lysozyme is a protein which is widely distributed in several human tissues and secretions including milk, tears and saliva. It has been demonstrated to hydrolyze linkages between N-acetylglucosamines. It has been demonstrated to be an inhibitor of chemotaxis and of the production of toxic oxygen free radicals and may also

have some role in the calcification process. As such, there is substantial interest in identifying novel polypeptides having homology to lysozyme. We describe herein the identification of a novel polypeptide which has sequence similarity to lysozyme.

35. PRO864

Wnt-4 is a secreted glycoprotein which correlates with, and is required for, kidney tubulogenesis. Mice lacking Wnt-4 activity fail to form pretubular cell aggregates; however, other aspects of mesenchymal and ureteric development are unaffected. Thus, Wnt-4 appears to act as an autoinducer of the mesenchyme to epithelial transition that underlies nephron development. Stark et al., Nature ;372(6507):679-683 (1994). In addition, members of the Wnt gene family code for cysteine-rich, secreted proteins, which are differentially expressed in the developing brain and possibly act as intercellular signaling molecules. A Wnt gene, e.g., Wnt-1 is known to be essential for specification of the midbrain cell fate. Yoshioka et al., Biochem. Biophys. Res. Commun. 203(3):1581-1588 (1994). Several member of the Wnt family of secreted factors are strongly implicated as regulators of mammary cellular growth and differentiation. Shimizu et al., Cell Growth Differ. 8(12) 1349-1358. Wnt-4 is normally expressed in early pregnancy. Wnt-4 may therefore be a local signal driving epithelial branching in pregnancy. Edwards PA, Biochem Soc Symp.63:21-34 (1998). See also, Lipschutz JH, Am. J. Kidney Dis. 31(3):383-397, (1998). We describe herein the identification and characterizaton of a novel polypeptide which has sequence similarity to Wnt-4, designated herein as PRO864.

36. PRO792

At least two cell-derived signals have been shown to be necessary for the induction of immunoglobulin isotype switching in B-cells. The first signal is given by either of the soluble lymphokines, interleukin (IL)-4 or IL-13, which induce germline epsilon transcript expression, but this alone is insufficient to trigger secretion of immunoglobulin E (IgE). The second signal is provided by a physical interaction between B-cells and activated T-cells, basophils and mast cells, and it has been shown that the CD40/CD40 ligand pairing is crucial for mediating IgE synthesis. Additionally, amongst the numerous pairs of surface adhesion molecules that are involved in IgE synthesis, the CD23/CD21 pair appears to play a key role in the generation of IgE. CD23 is a protein that is positively and negatively regulated by factors which increase or decrease IgE production, respectively. Antibodies to CD23 have been shown to inhibit IL-4-induced human IgE production *in vitro* and to inhibit antigen-specific IgE responses in a rat model, in an isotype selective manner (Bonnefoy et al., Eur. Respir. J. Suppl. 22:63S-66S (1996)). CD23 interacts with CD21 on B-cells, preferentially driving IgE production. Given that the CD23 protein plays an extremely important role in the induction of a mammalian IgE response, there is significant interest in identifying novel polypeptides having homology to CD23. We herein describe the identification and characterization of a novel polypeptide having homology to CD23, designated herein as PRO792.

37. PRO866

Mindin and spondin proteins are secreted proteins that are structurally related to one another and which have been identified in a variety of organisms. For example, Higashijima et al., Dev Biol. 192:211-227 (1997) have reported the identification of spondin and mindin expression in floor plate cells in the zebrafish embryonic axis, thereby suggesting that mindin and spondin prtoteins play important roles in embryonic development. This same group has reported that mindin and spondin proteins function as extracellular matrix proteins that have a high affinity for the basal lamina. (Id.). It has been reported that F-spondin is a secreted protein that promotes neural adhesion and neurite extension (Klar et al., Cell 69:95-110 (1992) and that M-spondin is an extracellular matrix protein that localizes to muscle attachment sites in Drosophila (Umemiya et al., Dev. Biol. 186:165-176 (1997)). Thus, there is significant inteest in identifying novel polypeptides having homology to the mindin and spondin proteins. We herein describe the identification and characterization of a novel polypeptide having homology to mindin2 and mindin1, designated herein as PRO866.

38. PRO871

Cyclophilins are a family of proteins that bind to cyclosporin A and possess peptidyl-prolyl cis-trans isomerase activity (Sherry et al., Proc. Natl. Acad. Sci. USA 95:1758-1763 (1998)). In addition, cyclophilins are secreted by activated cells and act in a cytokine-like manner, presumably via signaling through a cell surface cyclophilin receptor. Host cell-derived cyclophilin A has been shown to be incorporated into HIV-1 virions and its incorporation has been shown to be essential for viral infectivity. Thus, one or more the cyclophilins may be directly associated with HIV-1 infectivity. Given the obvious importance of the cyclophilin proteins, there is substantial interest in identifying novel polypeptides which have sequence homology to one or more of the cyclophilin proteins. We herein describe the identification and characterization of a novel polypeptide having homology to cyclophilin-like protein CyP-60, designated herein as PRO871.

39. PRO873

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Enzymes have also been shown to play important roles in combating various diseases and disorders. For example, liver carboxylesterases have been reported to assist in sensitizing human tumor cells to the cancer prodrugs. Danks *et al.*, report that stable expression of the cDNA encoding a carboxylesterase in Rh30 human rhabdomyosarcoma cells increased the sensitivity of the cells to the CPT-11 cancer prodrug 8.1-fold. Cancer Res. (1998) 58(1):20-22. The authors propose that this prodrug/enzyme combination could be exploited therapeutically in a manner analogous to approaches currently under investigation with the combinations of ganciclovir/herpes simplex virus thymidine kinase and 5-fluorocytosine/cytosine deaminase. van Pelt *et al.* demonstrated that a 55 kD human liver carboxylesterase inhibits the invasion of Plasmodium falciparum malaria sporozoites into primary human hepatocytes in culture. J Hepatol (1997) 27(4):688-698.

Carboxylesterases have also been found to be of importance in the detoxification of drugs, pesticides

and other xenobiotics. Purified human liver carboxylesterases have been shown to be involved in the metabolism of various drugs including cocaine and heroin. Prindel *et al.* describe the purification and cloning of a broad substrate specificity human liver carboxylesterase which catalyzes the hydrolysis of cocaine and heroin and which may play an important role in the degradation of these drugs in human tissues. J. Biol. Chem. (1997) 6:272(23):14769-14775. Brzenzinski *et al.* describe a spectrophotometric competitive inhibition assay used to identify drug or environmental esters that are metabolized by carboxylesterases. Drug Metab Dispos (1997) 25(9):1089-1096.

In light of the important physiological roles played by carboxylesterases, efforts are being undertaken by both industry and academia to identify new, native carboxylesterase homologs. We herein describe the identification and characterization of a novel polypeptide having homology to carboxylesterase, designated herein as PRO873.

40. PRO940

CD33 is a cell-surface protein that is a member of the sialoadhesin family of proteins that are capable of mediating sialic-acid dependent binding with distinct specificities for both the type of sialic acid and its linkage to subterminal sugars. CD33 is specifically expressed in early myeloid and some monocyte cell lineages and has been shown to be strongly associated with various myeloid tumors including, for example, acute non-lymphocytic leukemia (ANLL). As such, CD33 has been suggested as a potential target for the treatment of cancers associated with high level expression of the protein. There is, therefore, significant interest in the identification of novel polypeptides having homology to CD33. In fact, one CD33 homolog (designated CD33L) has already been identified and described (see Takei et al., Cytogenet. Cell Genet. 78:295-300 (1997)). We herein describe the identification of another novel polypeptide having homology to CD33, designated herein as PRO940. The novel polypeptide described herein also exhibits significant homology to the human OB binding proteins designated HSU71382_1 and HSU71383_1 in the Dayhoff database (version 35.45 SwissProt 35).

41. PRO941

Cadherins are a large family of transmembrane proteins. Cadherins comprise a family of calcium-dependent glycoproteins that function in mediating cell-cell adhesion in virtually all solid tissues of multicellular organisms. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been identified and characterized. Among the functions cadherins are known for, with some exceptions, are that cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Recently, it has been reported that while all cadherins share multiple repeats of a cadherin specific motif believed to correspond to folding of extracellular domains, members of the cadherin superfamily have divergent structures and, possibly, functions. In particular it has been reported that members of the cadherin superfamily are involved in signal transduction. See, Suzuki, J. Cell Biochem., 61(4):531-542 (1996). Cadherins are further described in Tanihara et al., J. Cell Sci., 107(6):1697-1704 (1994), Aberle et al., J. Cell Biochem., 61(4):514-523 (1996) and Tanihara et al., Cell

Adhes. Commun., 2(1):15-26 (1994). We herein describe the identification and characterization of a novel polypeptide having homology to a cadherin protein, designated herein as PRO941.

42. PRO944

Clostridium perfringens enterotoxin (CPE) is considered to be the virulence factor responsible for causing the symptoms of C. perfringens type A food poisoning and may also be involved in other human and veterinary illnesses (McClane, *Toxicon.* 34:1335-1343 (1996)). CPE carries out its adverse cellular functions by binding to an approximately 50 kD cell surface receptor protein designated the Clostridium perfringens enterotoxin receptor (CPE-R) to form an approximately 90,000 kD complex on the surface of the cell. cDNAs encoding the CPE-R protein have been identified characterized in both human and mouse (Katahira et al., *J. Cell Biol.* 136:1239-1247 (1997) and Katahira et al., *J. Biol. Chem.* 272:26652-26658 (1997)). Since the CPE toxin has been reported to cause a variety of illnesses in mammalian hosts and those illnesses are initiated by binding of the CPE toxin to the CPE-R, there is significant interest in identifying novel CPE-R homologs. We herein describe the identification and characterization of a novel polypeptide having homology to the CPE-R, designated herein as PRO944.

43. PRO983

Membrane-bound proteins include not only cell-surface membrane-bound proteins, but also proteins that are found on the surface of intracellular vesicles. These vesicles are involved in exocytosis, which is the fusion of secretory vesicles with the cellular plasma membrane, and have two main functions. One is the discharge of the vesicle contents into the extracellular space, and the second is the incorporation of new proteins and lipids into the plasma membrane itself. Exocytosis can be either constitutive or regulated. All eukaryotic cells exhibit constitutive exocytosis, which is marked by the immediate fusion of the secretory vesicle after formation. In contrast, regulated exocytosis results in the accumulation of the secretory vesicles that fuse with the plasma membrane upon receipt of an appropriate signal by vesicle-associated membrane proteins. Usually, this signal is an increase in the cytosolic free Ca^{2+} concentration. However, regulated exocytosis that is independent of Ca^{2+} has been reported (see, e.g. Fujita-Yoshigaki *et al.* J. Biol. Chem. (1996) 31:271(22):13130-13134). Regulated exocytosis is crucial to many specialized cells, including neurons (neurotransmitter release from synaptic vesicles), adrenal chromaffin cells (adrenaline secretion), pancreatic acinar cells (digestive enzyme secretion), pancreatic β-cells (insulin secretion), mast cells (histamine secretion), mammary cells (milk protein secretion), sperm (enzyme secretion), egg cells (creation of fertilization envelope) and adipocytes (insertion of glucose transporters into the plasma membrane).

Disorders involving exocytosis are known. For example, inflammatory mediator release from mast cells leads to a variety of disorders, including asthma. Similarly, Chediak-Higashi Syndrome (CHS) is a rare autosomal recessive disease in which neutrophils, monocytes and lymphocytes contain giant cytoplasmic granules. Accordingly, the proteins involved in exocytosis are of paramount interest and efforts are being undertaken by both industry and academia to identify new, vesicle-associated proteins. For example, Skehel *et*

al. identified a 33-kilodalton membrane protein in Aplysia, termed VAP-33, which is required for the exocytosis of neurotransmitter. Science (1995) 15:269(5230):1580-1583, and Neuropharmacology (1995) 34(11):1379-1385. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel vesicle- associated membrane proteins. It is an object of the invention to provide proteins having homology to the vesicle associated protein, VAP-33, designated herein as PRO983.

44. PRO1057

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized. The mammalian protease enzymes play important roles in many different biological processes including, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

In light of the important physiological roles played by protease enzymes, efforts are currently being undertaken by both industry and academia to identify new, native protease homologs. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. We herein describe the identification of novel polypeptides having homology to various protease enzymes, designated herein as PRO1057 polypeptides.

45. PRO1071

Thrombospondin-1 is a trimeric high molecular weight glycoprotein that is released from platelet alpha-granules in response to thrombin stimulation and that is also a transient component of the extracellular matrix in developing and repairing tissues (Adams, Int. J. Biochem. Cell Biol. 29:861-865 (1997) and Qian et al., Proc. Soc. Exp. Biol. Med. 212:199-207 (1996)). A variety of factors regulate thrombospondin expression and the protein is degraded by both extracellular and intracellular routes. Thrombospondin-1 functions as a cell adhesion molecule and also modulates cell movement, cell proliferation, neurite outgrowth and angiogenesis. As such, there is substantial interest in identifying novel polypeptides having homology to thrombospondin. We herein describe the identification and characterization of a novel polypeptide having homology to thrombospondin, designated herein as PRO1071.

46. PRO1072

Studies have reported that the redox state of the cell is an important determinant of the fate of the cell. Furthermore, reactive oxygen species have been reported to be cytotoxic, causing inflammatory disease, including tissue necrosis, organ failure, atherosclerosis, infertility, birth defects, premature aging, mutations and malignancy. Thus, the control of oxidation and reduction is important for a number of reasons, including the

control and prevention of strokes, heart attacks, oxidative stress, hypertension and may be associated with the development of malignancies. The levels of antioxidant enzymes, such as reductases, which catalyze the conversion of reactive oxygen species to water have been shown to be low in cancer cells. In particular, malignant prostate epithelium may have lowered expression of such antioxidant enzymes [Baker et al., Prostate 32(4):229-233 (1997)]. In this regard, reductases, are of interest. In addition, the transcription factors, NF-kappa B and AP-1, are known to be regulated by redox state and to affect the expression of a large variety of genes thought to be involved in the pathogenesis of AIDS, cancer, atherosclerosis and diabetic complications. Publications further describing this subject matter include Engman et al., Anticancer Res. (Greece), 17:4599-4605 (1997), Kelsey, et al., Br. J. Cancer, 76(7):852-854 (1997); Friedrich and Weiss, J. Theor. Biol., 187(4):529-40 (1997) and Pieulle, et al., J. Bacteriol., 179(18):5684-92 (1997). Given the physiological importance of redox reactions *in vivo*, efforts are currently being under taken to identify new, native proteins which are involved in redox reactions. We describe herein the identification of a novel polypeptide which has sequence similarity to reductase enzymes, desiignated herein as PRO1072.

47. PRO1075

Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct refolding of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNAse (Goldberger et al., *J. Biol. Chem.* 239:1406-1410 (1964) and Epstein et al., *Cold Sprring Harbor Symp. Quant. Biol.* 28:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus.

Given the importance of disulfide bond-forming enzymes and their potential uses in a number of different applications, for example in increasing the yield of correct refolding of recombinantly produced proteins, efforts are currently being undertaken by both industry and academia to identify new, native proteins having homology to protein disulfide isomerase. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel protein disulfide isomerase homologs. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. We herein describe a novel polypeptide having homology to protein disulfide isomerase, designated herein as PRO1075.

48. PRO181

In Drosophila, the dorsal-ventral polarity of the egg chamber depends on the localization of the oocyte nucleus and the gurken RNA to the dorsal-anterior corner of the oocyte. Gurken protein presumably acts as a ligand for the drosophila EGF receptor (torpedo/DER) expressed in the somatic follicle cells surrounding the oocyte. Cornichon is a gene required in the germline for dorsal-ventral signaling (Roth et al., Cell 81:967-978 (1995)). Cornichon, gurken and torpedo also function in an earlier signaling event that establishes posterior

follicle cell fates and specifies the anterior-posterior polarity of the egg chamber. Mutations in any or all of these genes prevent the formation of a correctly polarized microtubule cytoskeleton required for proper localization of the anterior and posterior determinants bicoid and oskar and for the asymmetric positioning of the oocyte nucleus. Thus, it is clear that the cornichon gene product plays an important role in early development. We herein describe the identification and characterization of a novel polypeptide having homology to the cornichon protein, designated herein as PRO181.

49. PRO195

Efforts arre currently being undertaken to identify and characterize novel transmembrane proteins. We herein describe the identification and characterization of a novel transmembrane polypeptide, designated herein as PRO195.

50. PRO865

Efforts arre currently being undertaken to identify and characterize novel secreted proteins. We herein describe the identification and characterization of a novel secreted polypeptide, designated herein as PRO865.

51. PRO827

VLA-2 is an cell-surface integrin protein that has been identified and characterized in a number of mammalian organisms, including both mouse and human. VLA-2 has been shown to be a receptor on the surface of cells for echovirus-1 (EV-1) which mediates infection of VLA-2-expressing cells by EV-1 (Zhang et al., Virology 235(2):293-301 (1997) and Bergelson et al., Science 255:1718-1720 (1992)). VLA-2 has also been shown to mediate the interaction of collagen with endothelium during *in vitro* vascular tube formation (Jackson et al., Cell Biol. Int. 18(9):859-867 (1994)). Various other integrin proteins that share various degrees of amino acid sequence homology with VLA-2 have been identified and characterized in a variety of mammalian organism. These integrins have been reported to play important roles in a variety of different physiological functions. Therefore, there is significant interest in identifying novel polypeptides having homology to one or more of the integrin proteins. We herein describe the identification and characterization of a novel polypeptide having homology to VLA-2 integrin protein, designated herein as PRO827.

52. PRO1114

Many important cytokine proteins have been identified and characterized and shown to signal through specific cell surface receptor complexes. For example, the class II cytokine receptor family (CRF2) includes the interferon receptors, the interleukin-10 receptor and the tissue factor CRFB4 (Spencer et al., J. Exp. Med. 187:571-578 (1998) and Kotenko et al., EMBO J. 16:5894-5903 (1997)). Thus, the multitude of biological activities exhibited by the various cytokine proteins is absolutely dependent upon the presence of cytokine receptor proteins on the surface of target cells. There is, therefore, a significant interest in identifying and characterizing novel polypeptides having homology to one or more of the cytokine receptor family. We herein

describe the identification and characterization of a novel polypeptide having homology to cytokine receptor family-4 proteins, designated herein as PRO1117.

Interferons (IFNs) encompass a large family of secreted proteins occurring in vertebrates. Although they were originally named for their antiviral activity, growing evidence supports a critical role for IFNs in cell growth and differentiation (Jaramillo et al., Cancer Investigation 13(3):327-338 (1995)). IFNs belong to a class of negative growth factors having the ability to inhibit the growth of a wide variety of cells with both normal and transformed phenotypes. IFN therapy has been shown to be beneficial in the treatment of human malignancies such as Karposi's sarcoma, chronic myelogenous leukemia, non-Hodgkin's lymphoma, and hairy cell leukemia as well as in the treatment of infectious diseases such as hepatitis B (Gamliel et al., Scanning Microscopy 2(1):485-492 (1988), Einhorn et al., Med. Oncol. & Tumor Pharmacother. 10:25-29 (1993), Ringenberg et al., Missouri Medicine 85(1):21-26 (1988), Saracco et al., Journal of Gastroenterology and Hepatology 10:668-673 (1995), Gonzalez-Mateos et al., Hepato-Gastroenterology 42:893-899 (1995) and Malaguarnera et al., Pharmacotherapy 17(5):998-1005 (1997)).

Interferons can be classified into two major groups based upon their primary sequence. Type I interferons, IFN-α and IFN-β, are encoded by a superfamily of intronless genes consisting of the IFN-α gene family and a single IFN-β gene that are thought to have arisen from a common ancestral gene. Type I interferons may be produced by most cell types. Type II IFN, or IFN-γ, is restricted to lymphocytes (T cells and natural killer cells) and is stimulated by nonspecific T cell activators or specific antigens *in vivo*.

Although both type I and type II IFNs produce similar antiviral and antiproliferative effects, they act on distinct cell surface receptors, wherein the binding is generally species specific (Langer et al., Immunol. Today 9:393-400 (1988)). Both IFN-α and IFN-β bind competitively to the same high affinity type I receptor, whereas IFN-γ binds to a distinct type II receptor. The presence and number of IFN receptors on the surface of a cell does not generally reflect the sensitivity of the cell to IFN, although it is clear that the effects of the IFN protein is mediated through binding to a cell surface interferon receptor. As such, the identification and characterization of novel interferon receptor proteins is of extreme interest.

We herein describe the identification and characterization of novel interferon receptor polypeptides, designated herein as "PRO1114 interferon receptor" polypeptides. Thus, the PRO1114 polypeptides of the present invention represents a novel cell surface interferon receptor.

53. PRO237

Carbonic anhydrase is an enzymatic protein that which aids carbon dioxide transport and release in the mammalian blood system by catalyzing the synthesis (and the dehydration) of carbonic acid from (and to) carbon dioxide and water. Thus, the actions of carbonic anhydrase are essential for a variety of important physiological reactions in the mammal. As such, there is significant interest in the identification and characterization of novel polypeptides having homology to carbonic anhydrase. We herein describe the identification and characterization of a novel polypeptide having homology to carbonic anhydrase, designated herein as PRO237.

54. PRO541

Numerous trypsin inhibitory proteins have been identified and characterized (see, e.g., Yamakawa et al., Biochim. Biophys. Acta 1395:202-208 (1998) and Mizuki et al., Mammalian Genome 3:274-280 (1992)). Trypsin inhibitor proteins play important roles in a variety of different physiological and biological pathways and are specifically involved in such processes as the regulation of protein degradation, digestion, and the like. Given the important roles played by such enzymatic proteins, there is significant interest in identifying and characterizing novel polypeptides having homology to known trypsin inhibitor proteins. We herein describe the identification and characterization of a novel polypeptide having homology to a trypsin inhibitor protein, designated herein as PRO541.

55. PRO273

Leukocytes include monocytes, macrophages, basophils, and eosinophils and play an important role in the immune response. These cells are important in the mechanisms initiated by T and/or B lymphocytes and secrete a range of cytokines which recruit and activate other inflammatory cells and contribute to tissue destruction.

Thus, investigation of the regulatory processes by which leukocytes move to their appropriate destination and interact with other cells is critical. Currently, leukocytes are thought to move from the blood to injured or inflamed tissues by rolling along the endothelial cells of the blood vessel wall. This movement is mediated by transient interactions between selectins and their ligands. Next, the leukocyte must move through the vessel wall and into the tissues. This diapedesis and extravasation step involves cell activation which promotes a more stable leukocyte-endothelial cell interaction, again mediated by integrins and their ligands.

Chemokines are a large family of structurally related polypeptide cytokines. These molecules stimulate leukocyte movement and may explain leukocyte trafficking in different inflammatory situations. Chemokines mediate the expression of particular adhesion molecules on endothelial cells, and they produce chemoattractants which activate specific cell types. In addition, the chemokines stimulate proliferation and regulate activation of specific cell types. In both of these activities, chemokines demonstrate a high degree of target cell specificity.

The chemokine family is divided into two subfamilies based on whether two amino terminal cysteine residues are immediately adjacent (C-C) or separated by one amino acid (C-X-C). Chemokines of the C-X-C family generally activate neutrophils and fibroblasts while the C-C chemokines act on a more diverse group of target cells including monocytes/macrophages, basophils, eosinophils and T lymphocytes. The known chemokines of both subfamilies are synthesized by many diverse cell types as reviewed in Thomson A. (1994) The Cytokine Handbook, 2 d Ed. Academic Press, N.Y. Chemokines are also reviewed in Schall TJ (1994) Chemotactic Cytokines: Targets for Therapeutic Development. International Business Communications, Southborough Mass. pp 180-270; and in Paul WE (1993) Fundamental Immunology, 3rd Ed. Raven Press, N.Y. pp 822-826.

Known chemokines of the C-X-C subfamily include macrophage inflammatory proteins alpha and beta (MIP-1 and MIP-2), interleukin-8 (IL-8), and growth regulated protein (GRO-alpha and beta).

MIP-2 was first identified as a 6 kDa heparin binding protein secreted by the mouse macrophage cell line RAW 264.7 upon stimulation with lipopolysaccharide (LPS). MIP-2 is a member of the C-X-C (or CXC) subfamily of chemokines. Mouse MIP-2 is chemotactic for human neutrophils and induces local neutrophil infiltration when injected into the foot pads of mice. Rat MIP-2 shows 86% amino acid homology to the mouse MIP-2 and is chemotactic for rat neutrophils but does not stimulate migration of rat alveolar macrophages or human peripheral blood eosinophils or lymphocytes. In addition, the rat MIP-2 has been shown to stimulate proliferation of rat alveolar epithelial cells but not fibroblasts.

Current techniques for diagnosis of abnormalities in inflamed or diseased issues mainly rely on observation of clinical symptoms or serological analyses of body tissues or fluids for hormones, polypeptides or various metabolites. Problems exist with these diagnostic techniques. First, patients may not manifest clinical symptoms at early stages of disease. Second, serological tests do not always differentiate between invasive diseases and genetic syndromes. Thus, the identification of expressed chemokines is important to the development of new diagnostic techniques, effective therapies, and to aid in the understanding of molecular pathogenesis.

To date, chemokines have been implicated in at least the following conditions: psoriasis, inflammatory bowel disease, renal disease, arthritis, immune-mediated alopecia, stroke, encephalitis, MS, hepatitis, and others. In addition, non-ELR-containing chemokines have been implicated in the inhibition of angiogenesis, thus indicating that these chemokines have a rule in tumor vascularization and tumorigenesis.

Therefore it is the object of this invention to identify polypeptides and nucleic acids encoding the same which have sequence identity and similarity with cytokine-induced neutrophil chemoattractants, MIP-1, MIP-2, and other related proteins. The efforts of this object are provided herein.

56. PRO701

Beta neurexins and neuroligins are plasma membrane proteins that are displayed on the neuronal cell surface. Neuroligin 1 is enriched in synaptic plasma membranes and acts as a splice site-specific ligand for beta neurexins as described in Ichtchenko, et al., Cell, 81(3):435-443 (1995). The extracellular sequence of neuroligin 1 is composed of a catalytically inactive esterase domain homologous to acetylcholinesterase. Neuroligin 2 and 3 are similar in structure and sequence to neuroligin 1. All neuroligins contain an N-terminal hydrophobic sequence with the characteristics of a cleaved signal peptide followed by a large esterase homology domain, a highly conserved single transmembrane region, and a short cytoplasmic domain. The three neuroligins are alternatively spliced at the same position and are expressed at high levels only in the brain. Tight binding of the three neuroligins to beta neurexins is observed only for beta neurexins lacking an insert in splice site 4. Thus, neuroligins constitute a multigene family of brain-specific proteins with distinct isoforms that may have overlapping functions in mediating recognition processes between neurons, see Ichtchenko, et al., J. Biol. Chem., 271(5):2676-2682 (1996). Moreover, neurexins and neuroligins have been reported as functioning as adhesion molecules in a Ca^{2+} dependent reaction that is regulated by alternative splicing of beta neurexins, i.e., see Nguyen and Sudhof, J. Biol. Chem., 272(41):26032-26039 (1997). Given the foregoing, membrane

bound proteins are of interest. More generally, membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound receptor proteins, particularly those having sequence identity and/or similarity with neuroligins 1, 2 and 3. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts are provided herein.

57. PRO704

VIP36 is localized to the Golgi apparatus and the cell surface, and belongs to a family of legume lectin homologues in the animal secretory pathway that might be involved in the trafficking of glycoproteins, glycolipids, or both. It is further believed that VIP36 binds to sugar residues of glycosphingolipids and/or gycosylphosphatidyl-inositol anchors and might provide a link between the extracellular/luminal face of glycolipid rafts and the cytoplasmic protein segregation machinery. Further regarding VIP36, it is believed that there is a signal at its C-terminus that matches an internalization consensus sequence which confers its ability to cycle between the plasma membrane and Golgi. See, Fiedler, et al, EMBO J., 13(7):1729-1740 (1994); Fiedler and Simons, J. Cell Sci., 109(1):271-276 (1996); Itin, et al., MBO J., 14(10):2250-2256 (1995). It is believed that VIP36 is either the same as or very closely related to the human GP36b protein. VIP36 and/or GP36b are of interest.

More generally, vesicular, cytoplasmic, extracellular and membrane-bound proteins play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information

received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Efforts are being undertaken by both industry and academia to identify new, native vesicular, cytoplasmic, secreted and membrane-bound receptor proteins, particularly those having sequence identity and/or similarity with VIP36. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

58. PRO706

Acid phophatase proteins are secreted proteins which dephophorylate terminal phosphate groups under acidic pH conditions. Acid phophatases contain a RHGXRXP amino acid sequence, which is predicted to be mechanistically significant. Acid phosphatases may have important functions in the diagnosis and treatment of human diseases. For example, prostatic acid phosphatase is a secreted protein uniquely expressed in prostatic tissue and prostate cancer. The level of prostatic acid phosphatase is a potential prognostic factor for local and biochemical control in prostate cancer patients treated with radiotherapy, as described in Lankford et al., Int. J. Radiat. Oncol. Biol. Phys. 38(2): 327-333 (1997). Research suggests that a cellular immune response to prostatic acid phosphatase may mediate destructive autoimmune prostatitis, and that xenogeneic forms of prostatic acid phosphatase may prove useful for immunotherapy of prostate cancer. See Fong et al., J. Immunol. 169(7): 3113-3117 (1997). Seminal prostatic acid phosphatase levels correlate significantly with very low sperm levels (oligospermia) in individuals over 35, see Singh et al., Singapore Med. J. 37(6): 598-599 (1996). Thus,

prostatic acid phosphatase has been implicated in a variety of human diseases, and may have an important function in diagnosis and therapy of these diseases. A series of aminobenzylphosphatic acid compounds are highly potent inhibitors of prostatic acid phosphatase, as described in Beers et al., Bioorg. Med. Chem. 4(10): 1693-1701 (1996).

More generally, extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those having sequence identity with prostate acid phosphatase precursor and lysosomal acid phosphatase precursor and in some cases, those having identity with DNA found in fetal heart. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

59. PRO707

Cadherins are a large family of transmembrane proteins. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been characterized. Among the functions cadherins are known for, with some exceptions, cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Cadherins are further described in Tanihara, et al., J. Cell Sci., 107(6):1697-1704 (1994) and Tanihara, et al., Cell Adhes. Commun., 2(1):15-26 (1994). Moreover, it has been reported that some members of the cadherin superfamily are involved in general cell-cell interaction processes including transduction. See, Suzuki, J. Cell Biochem., 61(4):531-542 (1996). Therefore, novel members of the cadherin superfamily are of interest.

More generally, all novel proteins are of interest, including membrane-bound proteins. Membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn,

received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, particularly membrane bound proteins having identity with cadherins. The results of such efforts are provided herein.

60. PRO322

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized, including the serine proteases which exhibit specific activity toward various serine-containing proteins. The mammalian protease enzymes play important roles in biological processes such as, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

Neuropsin is a novel serine protease whose mRNA is expressed in the central nervous system. Mouse neuropsin has been cloned, and studies have shown that it is involved in the hippocampal plasticity. Neuropsin has also been indicated as associated with extracellular matrix modifications and cell migrations. See, generally, Chen, et al., Neurosci., 7(2):5088-5097 (1995) and Chen, et al., J. Histochem. Cytochem., 46:313-320 (1998).

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound or secreted proteins, particularly those having homology to neuropsin, serine protease, neurosin and trypsinogen. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

61. PRO526

Protein-protein interactions include those involved with receptor and antigen complexes and signaling mechanisms. As more is known about the structural and functional mechanisms underlying protein-protein interactions, protein-protein interactions can be more easily manipulated to regulate the particular result of the protein-protein interaction. Thus, the underlying mechanisms of protein-protein interactions are of interest to the scientific and medical community.

All proteins containing leucine-rich repeats are thought to be involved in protein-protein interactions. Leucine-rich repeats are short sequence motifs present in a number of proteins with diverse functions and cellular locations. The crystal structure of ribonuclease inhibitor protein has revealed that leucine-rich repeats correspond to beta-alpha structural units. These units are arranged so that they form a parallel beta-sheet with one surface exposed to solvent, so that the protein acquires an unusual, nonglobular shape. These two features have been indicated as responsible for the protein-binding functions of proteins containing leucine-rich repeats. See, Kobe and Deisenhofer, Trends Biochem. Sci., 19(10):415-421 (Oct. 1994).

A study has been reported on leucine-rich proteoglycans which serve as tissue organizers, orienting and ordering collagen fibrils during ontogeny and are involved in pathological processes such as wound healing, tissue repair, and tumor stroma formation. Iozzo, R. V., Crit. Rev. Biochem. Mol. Biol., 32(2):141-174 (1997). Others studies implicating leucine rich proteins in wound healing and tissue repair are De La Salle, C., et al., Vouv. Rev. Fr. Hematol. (Germany), 37(4):215-222 (1995), reporting mutations in the leucine-rich motif in a complex associated with the bleeding disorder Bernard-Soulier syndrome, Chlemetson, K. J., Thromb. Haemost. (Germany), 74(1):111-116 (July 1995), reporting that platelets have leucine rich repeats and Ruoslahti, E. I., et al., WO9110727-A by La Jolla Cancer Research Foundation reporting that decorin binding to transforming growth factorβ has involvement in a treatment for cancer, wound healing and scarring. Related by function to this group of proteins is the insulin like growth factor (IGF), in that it is useful in wound-healing and associated therapies concerned with re-growth of tissue, such as connective tissue, skin and bone; in promoting body growth in humans and animals; and in stimulating other growth-related processes. The acid labile subunit (ALS) of IGF is also of interest in that it increases the half-life of IGF and is part of the IGF complex in vivo. ALS is further described in Leong and Baxter, Mol. Endocrinol., 6(6):870-876 (1992); Baxter, J. Biol. Chem., 264(20):11843-11848 (1989); and Khosravi, et al., J. Clin. Endocrinol. Metab., 82(12):3944-3951 (1997).

Another protein which has been reported to have leucine-rich repeats is the SLIT protein which has been reported to be useful in treating neuro-degenerative diseases such as Alzheimer's disease, nerve damage such as in Parkinson's disease, and for diagnosis of cancer, see, Artavanistsakonas, S. and Rothberg, J. M., WO9210518-A1 by Yale University. Also of interest is LIG-1, a membrane glycoprotein that is expressed specifically in glial cells in the mouse brain, and has leucine rich repeats and immunoglobulin-like domains. Suzuki, et al., J. Biol. Chem. (U.S.), 271(37):22522 (1996). Other studies reporting on the biological functions of proteins having leucine rich repeats include: Tayar, N., et al., Mol. Cell Endocrinol., (Ireland), 125(1-2):65-70 (Dec. 1996) (gonadotropin receptor involvement); Miura, Y., et al., Nippon Rinsho (Japan), 54(7):1784-1789 (July 1996) (apoptosis involvement); Harris, P. C., et al., J. Am. Soc. Nephrol., 6(4):1125-1133 (Oct. 1995)

(kidney disease involvement).

Efforts are therefore being undertaken by both industry and academia to identify new proteins having leucine rich repeats to better understand protein-protein interactions. Of particular interest are those proteins having leucine rich repeats and identity or similarity to known proteins having leucine rich repeats such as ALS. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound proteins having leucine rich repeats. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

62. PRO531

Cadherins are a large family of transmembrane proteins. Cadherins comprise a family of calcium-dependent glycoproteins that function in mediating cell-cell adhesion in virtually all solid tissues of multicellular organisms. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been characterized. Among the functions cadherins are known for, with some exceptions, cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Recently, it has been reported that while all cadherins share multiple repeats of a cadherin specific motif believed to correspond to folding of extracellular domains, members of the cadherin superfamily have divergent structures and, possibly, functions. In particular it has been reported that members of the cadherin superfamily are involved in signal transduction. See, Suzuki, J. Cell Biochem., 61(4):531-542 (1996). Cadherins are further described in Tanihara, et al., J. Cell Sci., 107(6):1697-1704 (1994), Aberle, et al., J. Cell Biochem., 61(4):514-523 (1996) and Tanihara, et al., Cell Adhes. Commun., 2(1):15-26 (1994).

Protocadherins are members of the cadherin superfamily which are highly expressed in the brain. In some studies, protocadherins have shown cell adhesion activity. See, Sano, et al., EMBO J., 12(6):2249-2256 (1993). However, studies have also shown that some protocadherins, such as protocadherin 3 (also referred to as Pcdh3 or pc3), do not show strong calcium dependent cell aggregation activity. See, Sago, et al., Genomics, 29(3):631-640 (1995) for this study and further characteristics of Pcdh3.

Therefore, novel members of the cadherin superfamily are of interest. More generally, all membrane-bound proteins and receptors are of interest. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is

regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are therefore being undertaken by both industry and academia to identify new, native membrane bound proteins, particular those having sequence identity with protocadherins, especially 3 and 4. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. Provided herein are the results of such efforts.

63. PRO534

Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct refolding of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNAse (Goldberger et al., J. Biol. Chem. 239:1406-1410 (1964) and Epstein et al., Cold Spring Harbor Symp. Quant. Biol. 28:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus. Protein disulfide isomerase and related proteins are further described in Laboissiere, et al., J. Biol. Chem., 270(47:28006-28009 (1995); Jeenes, et al., Gene, 193(2):151-156 (1997; Koivunen, et al., Genomics, 42(3):397-404 (1997); and Desilva, et al., DNA Cell Biol., 15(1):9-16 (1996). These studies indicate the importance of the identification of protein disulfide related proteins.

More generally, and also of interest are all novel membrane-bound proteins and receptors. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic

agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Given the importance of membrane bound proteins, efforts are under way to identity novel membrane bound proteins. Moreover, given the importance of disulfide bond-forming enzymes and their potential uses in a number of different applications, for example in increasing the yield of correct refolding of recombinantly produced proteins, efforts are currently being undertaken by both industry and academia to identify new, native proteins having sequence identity with protein disulfide isomerase. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel protein disulfide isomerase homologs. We herein describe a novel polypeptide having sequence identity with protein disulfide isomerase and the nucleic acids encoding the same.

64. PRO697

Secreted frizzled related proteins (sFRPs) are related to the frizzled family of transmembrane receptors. The sFRPs are approximately 30 kDa in size, and each contains a putative signal sequence, a frizzled-like cysteine-rich domain, and a conserved hydrophilic carboxy-terminal domain. It has been reported that sFRPs may function to modulate Wnt signaling, or function as ligands for certain receptors. Rattner, et al., PNAS USA, 94(7):2859-2863 (1997). Therefore, sFRPs and proteins having sequence identity and/or similarity to sFRPs are of interest.

Another secreted protein of interest is any member of the family of secreted apoptosis-related proteins (SARPs). Expression of SARPs modifies the intracellular levels of beta-catenin, suggesting that SARPs interfere with the Wnt-frizzled proteins signaling pathway. Melkonyan, et al., PNAS USA, 94(25):13636-13641 (1997). Therefore, SARPs and proteins having sequence identity and/or similarity to SARPs are of interest.

In addition to sFRPs and SARPs, many extracellular proteins are of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those having sequence identity or similarity with sFRP-2 and SARP-1. Many efforts are focused

on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

65. PRO717

Efforts are being undertaken by both industry and academia to identify new, native transmembrane receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts are provided herein.

66. PRO731

Cadherins are a large family of transmembrane proteins. Cadherins comprise a family of calcium-dependent glycoproteins that function in mediating cell-cell adhesion in virtually all solid tissues of multicellular organisms. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been characterized. Among the functions cadherins are known for, with some exceptions, cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Recently, it has been reported that while all cadherins share multiple repeats of a cadherin specific motif believed to correspond to folding of extracellular domains, members of the cadherin superfamily have divergent structures and, possibly, functions. In particular it has been reported that members of the cadherin superfamily are involved in signal transduction. See, Suzuki, J. Cell Biochem., 61(4):531-542 (1996). Cadherins are further described in Tanihara, et al., J. Cell Sci., 107(6):1697-1704 (1994), Aberle, et al., J. Cell Biochem., 61(4):514-523 (1996) and Tanihara, et al., Cell Adhes. Commun., 2(1):15-26 (1994).

Protocadherins are members of the cadherin superfamily which are highly expressed in the brain. In some studies, protocadherins have shown cell adhesion activity. See, Sano, et al., EMBO J., 12(6):2249-2256 (1993). However, studies have also shown that some protocadherins, such as protocadherin 3 (also referred to as Pcdh3 or pc3), do not show strong calcium dependent cell aggregation activity. See, Sago, et al., Genomics, 29(3):631-640 (1995) for this study and further characteristics of Pcdh3.

Therefore, novel members of the cadherin superfamily are of interest. More generally, all membrane-bound proteins and receptors are of interest. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze

that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are therefore being undertaken by both industry and academia to identify new, native membrane bound proteins, particular those having sequence identity with protocadherins, especially 4, 68, 43, 42, 3 and 5. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. Provided herein are the results of such efforts.

67. PRO218

Efforts are being undertaken by both industry and academia to identify new, native membrane bound proteins, particularly those having sequence identity with membrane regulator proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins.

68. PRO768

The integrins comprise a supergene family of cell-surface glycoprotein receptors that promote cellular adhesion. Each cell has numerous receptors that define its cell adhesive capabilities. Integrins are involved in a wide variety of interaction between cells and other cells or matrix components. The integrins are of particular importance in regulating movement and function of immune system cells. The platelet IIb/IIIA integrin complex is of particular importance in regulating platelet aggregation. A member of the integrin family, integrin β-6, is expressed on epithelial cells and modulates epithelial inflammation. Another integrin, leucocyte-associated antigen-1 (LFA-1) is important in the adhesion of lymphocytes during an immune response.

Of particular interest is H36-alpha 7, an integrin alpha chain that is developmentally regulated during myogenesis as described in Song, et al., J. Cell Biol., 117(3):643-657 (1992). The expression pattern of the laminin-binding alpha 7 beta 1 integrin is developmentally regulated in skeletal, cardiac, and smooth muscle. Ziober, et al., Mol. Biol. Cell, 8(9):1723-1734 (1997). It has been reported that expression of the alpha 7-X1/X2 integrin is a novel mechanism that regulates receptor affinity states in a cell-specific context and may modulate integrin-dependent events during muscle development and repair. Id. It has further been reported that laminins promote the locomotion of skeletal myoblasts via the alpha 7 integrin receptor. In particular it was reported that alpha 7 beta 1 receptor can promote myoblast adhesion and motility on a restricted number of laminin isoforms and may be important in myogenic precursor recruitment during regeneration and differentiation. Yao, et al., J. Cell Sci., 109(13):3139-3150 (1996). Spliced variants of integrin alpha 7 are also described in Leung, et al., Biochem. Biophys. Res. Commun., 243(1):317-325 (1998) and Fornaro and

Languino, Matrix Biol., 16(4):185-193 (1997). Moreover, it has been reported that absence of integrin alpha 7 causes a form of muscular dystrophy. Thus integrins, particularly those related to integrin 7 and related molecules, are of interest.

In addition to the interest of integrins, more generally, all membrane-bound proteins and receptors are of interest since such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Therefore, efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts, particularly those focused on identifying new polypeptides having sequence identity with integrins, are provided herein.

69. PRO771

Testican is a multidomain testicular proteoglycan which is expressed in numerous tissue types including, but not limited to neuromuscular tissue, the brain and reproductive tissues. Testican resembles modulators of cell social behavior such as the regulation of cell shape, adhesion, migration and proliferation. [Bonnet, F. et al., J. Biol. Chem., 271(8):4373 (1996), Perin, J.P. et al., EXS (Switzerland), 70:191 (1994), Alliel, P.M., et al, Eur. J. Biochem., 214(1):346 (1993), Charbonnier, F., et al., C. R. Seances Soc. Biol. Fil. (France), 191(1):127 (1997)]. Among other reasons, since testican has been implicated in neuronal processes and may be associated with the growth of connective tissue, testican and related molecules are of interest.

More generally, all extracellular proteins are of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted

polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts, particularly those focused on identifying molecules having identity and/or similarity with testican are of interest.

70. PRO733

T1/ST2 is a receptor-like molecule homologous to the type I interleukin-1 receptor, believed to be involved in cell signaling. The T1/ST2 receptor and/or putative ligands are further described in Gayle, et al., J. Biol. Chem., 271(10):5784-5789 (1996), Kumar, et al., J. Biol. Chem., 270(46):27905-27913 (1995), and Mitcham, et al., J. Biol. Chem., 271(10):5777-5783 (1996). These proteins, and proteins related thereto are of interest.

More generally all membrane-bound proteins and receptors are of interest since they can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor proteins.

Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts are provided herein.

71. PRO162

Pancreatitis-associated protein (PAP) is a secretory protein that is overexpressed by the pancreas during acute pancreatitis. Serum PAP concentrations have been shown to be abnormally high in patients with acute pancreatitis. Pezzilli et al., Am. J. Gastroenterol., 92(10):1887-1890 (1997).

PAP is synthesized by the pancreas due to pancreatic inflammation and has been shown to be a good serum marker for injury of the pancreas. In addition, serum PAP levels appear to strongly correlate with creatinine clearance measurements. In patients with a pancreas-kidney transplantation, PAP may prove to be a useful biological and histological marker of pancreatic graft rejection. Van der Pijl et al., Transplantation, 63(7):995-1003 (1997). Further, PAP has been shown to be useful in screening neonates for cystic fibrosis. In fact, PAP may discriminate cystic fibrosis neonates with better specificity than the current immunoreactive trypsis assay. Iovanna et al., C. R. Acad. Aci. III, 317(6):561-564.

Secreted proteins such as PAP have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts are presented herein.

72. PRO788

Anti-neoplastic urinary protein (ANUP) was identified as the major protein present in a fraction of human urine which exhibits antiproliferative activity against human tumor cell lines without affecting the growth of several normal diploid cell lines or tumor cells of mouse or hamster origin. Sloane et al., Biochem. J., 234(2):355-362 (1986).

ANUP is a unique cytokine that has been found in human granulocytes. The N-terminal amino acid sequence has been shown to be unique. A synthetic peptide corresponding to the first nine residues, with Cys at positions 4 and 7, was found to be an anti-tumor agent in vitro. Ridge and Sloane, Cytokine, 8(1):1-5 (1996).

Secreted proteins such as ANUP have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

73. PRO1008

Dickkopf-1 (dkk-1) is a member of a family of secreted proteins and functions in head induction. Dkk-1 is an inducer of Spemann organizer in amphibian embryos. Glinka, et al., Nature, 391(6665):357-362 (1998). Dkk-1 is a potent antagonist of Wnt signalling, suggesting that dkk genes encode a family of secreted Wnt inhibitors. Thus, dkk-1 family members and related molecules are of interest.

More generally, all extracellular proteins are of interest since they can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those related to dkk-1. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts to identify molecules related to dkk-1 are provided herein.

74. PRO1012

Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct refolding of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNAse (Goldberger et al., J. Biol. Chem. 239:1406-1410 (1964) and Epstein et al., Cold Spring Harbor Symp. Quant. Biol. 28:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus. Protein disulfide isomerase and related proteins are further described in Laboissiere,

et al., J. Biol. Chem., 270(47:28006-28009 (1995); Jeenes, et al., Gene, 193(2):151-156 (1997; Koivunen, et al., Genomics, 42(3):397-404 (1997); and Desilva, et al., DNA Cell Biol., 15(1):9-16 (1996). These studies indicate the importance of the identification of protein disulfide related proteins.

More generally, the identification of all extracellular and membrane-bound proteins is of interest since they play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Of particular interest are cellular proteins having endoplasmic reticulum (ER) retention signals. These proteins are retained in the cell and function closely with endoplasmic reticulum in protein production. Such proteins have been described previously, i.e., see Shorrosh and Dixon, Plant J., 2(1):51-58 (1992).

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, and in particular, cellular proteins having ER retension signals. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts, particularly the identification of novel polypeptides and nucleic acids encoding the same, which have sequence identity and similarity to protein disulfide isomerase are presented herein.

75. PRO1014

Oxygen free radicals and antioxidants appear to play an important role in the central nervous system after cerebral ischemia and reperfusion. Moreover, cardiac injury, related to ischaemia and reperfusion has been reported to be caused by the action of free radicals. Additionally, studies have reported that the redox state of the cell is a pivotal determinant of the fate of the cells. Furthermore, reactive oxygen species have been reported to be cytotoxic, causing inflammatorydisease, including tissue necrosis, organ failure, atherosclerosis, infertility, birth defects, premature aging, mutations and malignancy. Thus, the control of oxidation and reduction is important for a number of reasons including for control and prevention of strokes, heart attacks, oxidative stress and hypertension. In this regard, reductases, and particularly, oxidoreductases, are of interest. Publications further describing this subject matter include Kelsey, et al., Br. J. Cancer, 76(7):852-4 (1997); Friedrich and Weiss, J. Theor. Biol., 187(4):529-40 (1997) and Pieulle, et al., J. Bacteriol., 179(18):5684-92 (1997).

In addition to reductases in particular, novel polypeptides are generally of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts, particularly those identifying polypeptides having sequence identity with reductases, and the nucleic acids encoding the same, are presented herein.

76. PRO1017

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Sulfotransferases are enzymes which transfer sulfate from a sulfate donor to acceptor substrates, particularly those containing terminal glucoronic acid. The HNK-1 carbohydrate epitope is expressed on several neural adhesion glycoproteins and a glycolipid, and is involved in cell interactions. The

glucuronyltransferase and sulfotransferase are considered to be the key enzymes in the biosynthesis of this epitope because the rest of the structure occurs often in glycoconjugates. HNK-1 sulfotransfererase is further described in Bakker, H., et al., J. Biol. Chem., 272(47):29942-29946 (1997).

In addition to HNK-1 sulfotransfererase, and novel proteins related thereto, all novel proteins are of interest. Extracellular and membrane-bound proteins play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, particularly those having sequence identity with HNK-1 sulfotransferase. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts are provided herein.

77. PRO474

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Glucose dehydrogenase functions in the oxidation of glucose to gluconate to generate metabolically useful energy. The regulation of the PQQ-linked glucose dehydrogenase in different organisms is reviewed in Neijssel, et al., Antonie Van Leeuwenhoek, 56(1):51-61 (1989). Glucose dehydrogenase

functions as an auxiliary energy generating mechanism, because it is maximally synthesized under conditions of energy stress. In addition to molecules related to glucose dehydrogenase, all novel proteins are of interest. Extracellular and membrane-bound proteins play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, and particularly cellular proteins and those related to dehydrogenase or oxidoreductase. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts are presented herein.

78. PRO1031

It has been reported that the cytokine interleukin 17 (IL-17) stimulates epithelial, endothelial, and fibroblastic cells to secrete cytokines such as IL-6, IL-8, and granulocyte-colony-stimulating factor, as well as prostaglandin E2. Moreover, it has been shown that when cultured in the presence of IL-17, fibroblasts could sustain proliferation of CD34+ preferential maturation into neutrophils. Thus it has been suggested that IL-17 constitutes an early initiator of the T cell-dependent inflammatory reaction and/or an element of the cytokine network that bridges the immune system to hematopoiesis. See, Yao, et al., J. Immunol., 155(12):5483-5486 (1995); Fossiez, et al., J. Exp. Med., 183(6):2593-2603 (1996); Kennedy, et al., J. Interferon Cytokine Res.,

16(8):611-617 (1996). Thus, proteins related to IL-17 are of interest.

More generally, all novel proteins are of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those related to IL-17. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637)]. The results of such efforts are presented herein.

79. PRO938

Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct refolding of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNAse (Goldberger et al., J. Biol. Chem. 239:1406-1410 (1964) and Epstein et al., Cold Spring Harbor Symp. Quant. Biol. 28:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus. Protein disulfide isomerase and related proteins are further described in Laboissiere, et al., J. Biol. Chem., 270(47):28006-28009 (1995); Jeenes, et al., Gene, 193(2):151-156 (1997); Koivunen, et al., Genomics, 42(3):397-404 (1997); Desilva, et al., DNA Cell Biol., 15(1):9-16 (1996); Freedman, et al. Trends in Biochem. Sci. 19:331-336 (1994); Bulleid, N.J. Advances in Prot. Chem. 44:125-50 (1993); and Noiva, R., Prot. Exp. and Purification 5:1-13 (1994). These studies indicate the importance of the identification of protein disulfide related proteins.

More generally, and also of interest are all novel membrane-bound proteins and receptors. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors,

cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Given the importance of membrane bound proteins, efforts are under way to identity novel membrane bound proteins. Moreover, given the importance of disulfide bond-forming enzymes and their potential uses in a number of different applications, for example in increasing the yield of correct refolding of recombinantly produced proteins, efforts are currently being undertaken by both industry and academia to identify new, native proteins having sequence identity with protein disulfide isomerase. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel protein disulfide isomerase homologs.

We herein describe the identification and characterization of a novel polypeptide having homology to protein disulfide isomerase.

80. PRO1082

The low density lipoprotein (LDL) receptor is a membrane-bound protein that plays a key role in cholesterol homeostasis, mediating cellular uptake of lipoprotein particles by high affinity binding to its ligands, apolipoprotein (apo) B-100 and apoE. The ligand-binding domain of the LDL receptor contains 7 cysteine-rich repeats of approximately 40 amino acids, wherein each repeat contains 6 cysteines, which form 3 intra-repeat disulfide bonds. These unique structural features provide the LDL receptor with its ability to specifically interact with apo B-100 and apoE, thereby allowing for transport of these lipoprotein particles across cellular membranes and metabolism of their components. Soluble fragments containing the extracellular domain of the LDL receptor have been shown to retain the ability to interact with its specific lipoprotein ligands (Simmons et al., J. Biol. Chem. 272:25531-25536 (1997)). LDL receptors are further described in Javitt, FASEB J., 9(13):1378-1381 (1995) and Herz and Willnow, Ann. NY Acad. Sci., 737:14-19 (1994). Thus, proteins having sequence identity with LDL receptors are of interest.

More generally, all membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides

(for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor. Of particular interest are membrane bound proteins that have type II transmembrane domains.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are thus being undertaken by both industry and academia to identify new, native proteins, particularly membrane bound proteins including type II transmembrane bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts are provided herein.

81. PRO1083

Of particular interest are membrane bound proteins that belong to the seven transmembrane (7TM) receptor superfamily. Examples of these receptors include G-protein coupled receptors such as ion receptors. Another example of a 7TM receptor superfamily member is described in Osterhoff, et al., DNA Cell Biol., 16(4):379-389 (1997).

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. The results of such efforts are presented herein.

82. PRO200

Polypeptides involved in survival, proliferation and/or differentiation of cells are of interest. Polypeptides known to be involved in the survival, proliferation and/or differentiation of cells include VEGF and members of the bone morphogenetic protein family. Therefore, novel polypeptides which are related to either VEGF or the bone morphogenetic protein are of interest.

The heparin-binding endothelial cell-growth factor, VEGF, was identified and purified from media conditioned by bovine pituitary follicular or folliculo-stellate cells over several years ago. See Ferrara *et al.*, *Biophys. Res. Comm. 161*, 851 (1989). VEGF is a naturally occurring compound that is produced in follicular or folliculo-stellate cells (FC), a morphologically well characterized population of granular cells. The FC are stellate cells that send cytoplasmic processes between secretory cells.

VEGF is expressed in a variety of tissues as multiple homodimeric forms (121, 165, 189 and 206 amino acids per monomer) resulting from alternative RNA splicing. $VEGF_{121}$ is a soluble mitogen that does not bind heparin; the longer forms of VEGF bind heparin with progressively higher affinity. The heparin-binding forms of VEGF can be cleaved in the carboxy terminus by plasmin to release (a) diffusible form(s) of VEGF. Amino acid sequencing of the carboxy terminal peptide identified after plasmin cleavage is Arg_{110}-Ala_{111}. Amino terminal "core" protein, VEGF (1-110) isolated as a homodimer, binds neutralizing monoclonal antibodies (4.6.1 and 2E3) and soluble forms of FMS-like tyrosine kinase (FLT-1), kinase domain region (KDR) and fetal liver kinase (FLK) receptors with similar affinity compared to the intact $VEGF_{165}$ homodimer.

As noted, VEGF contains two domains that are responsible respectively for binding to the KDR and FLT-1 receptors. These receptors exist only on endothelial (vascular) cells. As cells become depleted in oxygen, because of trauma and the like, VEGF production increases in such cells which then bind to the respective receptors in order to signal ultimate biological effect. The signal then increases vascular permeability and the cells divide and expand to form new vascular pathways - vasculogenesis and angiogenesis.

Thus, VEGF is useful for treating conditions in which a selected action on the vascular endothelial cells, in the absence of excessive tissue growth, is important, for example, diabetic ulcers and vascular injuries resulting from trauma such as subcutaneous wounds. Being a vascular (artery and venus) endothelial cell growth factor, VEGF restores cells that are damaged, a process referred to as vasculogenesis, and stimulates the formulation of new vessels, a process referred to as angiogenesis.

VEGF would also find use in the restoration of vasculature after a myocardial infarct, as well as other uses that can be deduced. In this regard, inhibitors of VEGF are sometimes desirable, particularly to mitigate processes such as angiogenesis and vasculogenesis in cancerous cells.

Regarding the bone morphogenetic protein family, members of this family have been reported as being involved in the differentiation of cartilage and the promotion of vascularization and osteoinduction in preformed hydroxyapatite. Zou, et al., Genes Dev. (U.S.), 11(17):2191 (1997); Levine, et al., Ann. Plast. Surg., 39(2):158 (1997). A number of related bone morphogenetic proteins have been identified, all members of the bone morphogenetic protein (BMP) family. Bone morphogenetic native and mutant proteins, nucleic acids encoding therefor, related compounds including receptors, host cells and uses are further described in at least: U.S. Patent Nos. 5,670,338; 5,454,419; 5,661,007; 5,637,480; 5,631,142; 5,166,058; 5,620,867; 5,543,394; 4,877,864; 5,013,649; 55,106,748; and 5,399,677. Of particular interest are proteins having homology with bone morphogenetic protein 1, a procollagen C-proteinase that plays key roles in regulating matrix deposition.

The present invention is predicated upon research intended to identify novel polypeptides which are related to VEGF and the BMP family, and in particular, polypeptides which have a role in the survival,

proliferation and/or differentiation of cells. While the novel polypeptides are not expected to have biological activity identical to the known polypeptides to which they have homology, the known polypeptide biological activities can be used to determine the relative biological activities of the novel polypeptides. In particular, the novel polypeptides described herein can be used in assays which are intended to determine the ability of a polypeptide to induce survival, proliferation or differentiation of cells. In turn, the results of these assays can be used accordingly, for diagnostic and therapeutic purposes. The results of such research is the subject of the present invention.

83. PRO285 and PRO286

The cloning of the Toll gene of *Drosophila*, a maternal effect gene that plays a central role in the establishment of the embryonic dorsal-ventral pattern, has been reported by Hashimoto *et al.*, Cell 52, 269-279 (1988). The *Drosophila* Toll gene encodes an integral membrane protein with an extracytoplasmic domain of 803 amino acids and a cytoplasmic domain of 269 amino acids. The extracytoplasmic domain has a potential membrane-spanning segment, and contains multiple copies of a leucine-rich segment, a structural motif found in many transmembrane proteins. The Toll protein controls dorsal-ventral patterning in *Drosophila* embryos and activates the transcription factor Dorsal upon binding to its ligand Spätzle. (Morisato and Anderson, Cell 76, 677-688 (1994).) In adult *Drosophila*, the Toll/Dorsal signaling pathway participates in the anti-fungal immune response. (Lenaitre et al., Cell 86, 973-983 (1996).)

A human homologue of the *Drosophila* Toll protein has been described by Medzhitov et al., Nature 388, 394-397 (1997). This human Toll, just as *Drosophila* Toll, is a type I transmembrane protein, with an extracellular domain consisting of 21 tandemly repeated leucine-rich motifs (leucine-rich region - LRR), separated by a non-LRR region, and a cytoplasmic domain homologous to the cytoplasmic domain of the human interleukin-1 (IL-1) receptor. A constitutively active mutant of the human Toll transfected into human cell lines was shown to be able to induce the activation of NF-κB and the expression of NF-κB-controlled genes for the inflammatory cytokines IL-1, IL-6 and IL-8, as well as the expression of the constimulatory molecule B7.1, which is required for the activation of native T cells. It has been suggested that Toll functions in vertebrates as a non-clonal receptor of the immune system, which can induce signals for activating both an innate and an adaptive immune response in vertebrates. The human Toll gene reported by Medzhitov et al., *supra* was most strongly expressed in spleen and peripheral blood leukocytes (PBL), and the authors suggested that its expression in other tissues may be due to the presence of macrophages and dendritic cells, in which it could act as an early-warning system for infection. The public GenBank database contains the following Toll sequences: Toll1 (DNAX# HSU88540-1, which is identical with the random sequenced full-length cDNA #HUMRSC786-1); Toll2 (DNAX# HSU88878-1); Toll3 (DNAX# HSU88879-1); and Toll4 (DNAX# HSU88880-1, which is identical with the DNA sequence reported by Medzhitov et al., *supra*). A partial Toll sequence (Toll5) is available from GenBank under DNAX# HSU88881-1.

Further human homologues of the Drosophila Toll protein, designated as Toll-like receptors (huTLRs1-5) were recently cloned and shown to mirror the topographic structure of the Drosophila counterpart (Rock *et*

al., Proc. Natl. Acad. Sci. USA 95, 588-593 [1998]). Overexpression of a constitutively active mutant of one human TLR (Toll-protein homologue - Medzhitov *et al.*, *supra*; TLR4 - Rock *et al.*, *supra*) leads to the activation of NF-κB and induction of the inflammatory cytokines and constimulatory molecules. Medzhitov *et al.*, *supra*.

84. PRO213-1, PRO1330 and PRO1449

Cancer is characterized by the increase in the number of abnormal, or neoplastic, cells derived from a normal tissue which proliferate to form a tumor mass, the invasion of adjacent tissues by these neoplastic tumor cells, and the generation of malignant cells which eventually spread via the blood or lymphatic system to regional lymph nodes and to distant sites (metastasis). In a cancerous state a cell proliferates under conditions in which normal cells would not grow. Cancer manifests itself in a wide variety of forms, characterized by different degrees of invasiveness and aggressiveness.

Alteration of gene expression is intimately related to the uncontrolled cell growth and de-differentiation which are a common feature of all cancers. The genomes of certain well studied tumors have been found to show decreased expression of recessive genes, usually referred to as tumor suppression genes, which would normally function to prevent malignant cell growth, and/or overexpression of certain dominant genes, such as oncogenes, that act to promote malignant growth. Each of these genetic changes appears to be responsible for importing some of the traits that, in aggregate, represent the full neoplastic phenotype (Hunter, Cell 64, 1129 [1991]; Bishop, Cell 64, 235-248 [1991]).

A well known mechanism of gene (e.g. oncogene) overexpression in cancer cells is gene amplification. This is a process where in the chromosome of the ancestral cell multiple copies of a particular gene are produced. The process involves unscheduled replication of the region of chromosome comprising the gene, followed by recombination of the replicated segments back into the chromosome (Alitalo et al., Adv. Cancer Res. 47, 235-281 [1986]). It is believed that the overexpression of the gene parallels gene amplification, i.e. is proportionate to the number of copies made.

Proto-oncogenes that encode growth factors and growth factor receptors have been identified to play important roles in the pathogenesis of various human malignancies, including breast cancer. For example, it has been found that the human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185-kd transmembrane glycoprotein receptor (p185HER2; HER2) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer (Slamon et al., Science 235:177-182 [1987]; Slamon et al., Science 244:707-712 [1989]).

It has been reported that gene amplification of a protooncogene is an event typically involved in the more malignant forms of cancer, and could act as a predictor of clinical outcome (Schwab et al., Genes Chromosomes Cancer 1, 181-193 [1990]; Alitalo et al., supra). Thus, erbB2 overexpression is commonly regarded as a predictor of a poor prognosis, especially in patients with primary disease that involves axillary lymph nodes (Slamon et al., [1987] and [1989], supra; Ravdin and Chamness, Gene 159:19-27 [1995]; and Hynes and Stern, Biochem Biophys Acta 1198: 165-184 [1994]), and has been linked to sensitivity and/or

resistance to hormone therapy and chemotherapeutic regimens, including CMF (cyclophosphamide, methotrexate, and fluoruracil) and anthracyclines (Baselga et al., Oncology 11 (3 Suppl 1): 43-48 [1997]). However, despite the association of erbB2 overexpression with poor prognosis, the odds of HER2-positive patients responding clinically to treatment with taxanes were greater than three times those of HER2-negative patients (Ibid). A recombinant humanized anti-ErbB2 (anti-HER2) monoclonal antibody (a humanized version of the murine anti-ErbB2 antibody 4D5, referred to as rhuMAb HER2 or Herceptin 7ð) has been clinically active in patients with ErbB2-overexpressing metastatic breast cancers that had received extensive prior anticancer therapy. (Baselga et al., J. Clin. Oncol. 14:737-744 [1996]).

The protein Notch and its homologues are key regulatory receptors in determining the cell fate in various development processes. The protein Notch-4, also known as int-3 oncogene, was originally identified as a frequent target in mouse mammary tumor virus (MMVS). Notch-4 is believed to be a transgene which affects the differentiation capacity of stem cells and leads to neoplastic proliferation in epithelial cells. Shirayoshi et al., Genes Cells 2(3): 213-224 (1997). During embryogenesis, the expression of Notch-4 was detected in endothelial cells of blood vessels forming tissues such as the dorsal aorta, intersegmental vessels, yolk sac vessels, cephalic vessels, heart, vessels in branchial arches, and capillary plexuses. Notch-4 expression in these tissues was also associated with flk-1, the major regulatory gene of vasculogenesis and angiogenesis. Notch-4 is also upregulated in vitro during the differentiation of endothelial stem cell. The endothelial cell specific expression pattern of Notch-4, as well as its structural similarity to Notch suggest that Notch-4 is an endothelial cell specific homologue of Notch and that it may play a role in vaculogenesis and angiogenesis.

85. PRO298

Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO298 polypeptides.

86. PRO337

Neuronal development in higher vertebrates is characterized by processes that must successfully navigate distinct cellular environment en route to their synaptic targets. The result is a functionally precise formation of neural circuits. The precision is believed to result form mechanisms that regulate growth cone pathfinding and target recognition, followed by latter refinement and remodeling of such projections by events that require neuronal activity, Goodman and Shatz, Cell/Neuron [Suppl.] 72(10): 77-98 (1993). It is further evident that different neurons extend nerve fibers that are biochemically distinct and rely on specific guidance cues provided by cell-cell, cell-matrix, and chemotrophic interactions to reach their appropriate synaptic targets, Goodman et al., supra.

One particular means by which diversity of the neuronal cell surface may be generated is through differential expression of cell surface proteins referred to as cell adhesion molecules (CAMs). Neuronally

expressed CAMs have been implicated in diverse developmental processes, including migration of neurons along radial glial cells, providing permissive or repulsive substrates for neurite extension, and in promoting the selective fasciculation of axons in projectional pathways. Jessel, Neuron 1: 3-13 (1988); Edelman and Crossin, Annu. Rev. Biochem. 60: 155-190 (1991). Interactions between CAMs present on the growth cone membrane and molecules on opposing cell membranes or in the extracellular matrix are thought to provide the specific guidance cues that direct nerve fiber outgrowth along appropriate projectional pathways. Such interactions are likely to result in the activation of various second messenger systems within the growth cone that regulate neurite outgrowth. Doherty and Walsh, Curr. Opin Neurobiol. 2: 595-601 (1992).

In higher vertebrates, most neural CAMs have been found to be members of three major structural families of proteins: the integrins, the cadherins, and the immunoglobulin gene superfamily (IgSF). Jessel, supra.; Takeichi, Annu. Rev. Biochem. 59: 237-252 (1990); Reichardt and Tomaselli, Annu. Rev. Neurosci. 14: 531-570 (1991). Cell adhesion molecules of the IgSF (or Ig-CAMs), in particular, constitute a large family of proteins frequently implicated in neural cell interactions and nerve fiber outgrowth during development, Salzer and Colman, Dev. Neurosci. 11: 377-390 (1989); Brümmendorf and Rathjen, J. Neurochem. 61: 1207-1219 (1993). However, the majority of mammalian Ig-CAMs appear to be too widely expressed to specify navigational pathways or synaptic targets suggesting that other CAMs, yet to be identified, have role in these more selective interactions of neurons.

Many of the known neural Ig-CAMs have been found to be attached to the plasma membrane via a glycosylphosphatidylinositol (GPI) anchor. Additionally, many studies have implicated GPI-anchored proteins in providing specific guidance cues during the outgrowth on neurons in specific pathways. In studies of the grasshopper nervous system, treatment of embryos with phosphatidylinositol-specific phopholipase C (PIPLC), which selectively removes GPI-anchored proteins from the surfaces of cells, resulted in misdirection and faulty navigation among subsets of pioneering growth cones, as well as inhibited migratory patterns of a subset of early neurons, Chang et al., Devel. 114: 507-519 (1992). The projection of retinal fibers to the optic tectum appears to depend, in part, on a 33 kDa GPI-anchored protein, however, the precise nature of this protein is unknown. Stahl et al., Neuron 5: 735-743 (1990).

The expression of various GPI-anchored proteins has been characterized amongst the different populations of primary rat neurons amongst dorsal root ganglion, sympathetic neurons of the cervical ganglion, sympathetic neurons of the superior cervical ganglion, and cerebellar granule neurons. Rosen et al., J. Cell Biol. 117: 617-627 (1992). In contrast to the similar pattern of total membrane protein expression by these different types of neurons, striking differences were observed in the expression of GPI-anchored proteins between these neurons. Recently, a 65 kDa protein band known as neurotrimin was discovered and found to be differentially expressed by primary neurons (Rosen et al., supra), and restricted to the nervous system and found to be the most abundant and earliest expressed of the GPI-anchored species in the CNS. Struyk et al., J. Neuroscience 15(3): 2141-2156 (1995). The discovery of neurotrimin has further lead to the identification of a family of IgSF members, each containing three Ig-like domains that share significant amino acid identity, now termed IgLON. Struyk et al., supra; Pimenta et al., Gene 170(2): 189-95 (1996).

Additional members of the IgLON subfamily include opiate binding cell adhesion molecule (OBCAM), Schofield et al., EMBO J. 8: 489-495 (1989); limbic associated membrane protein (LAMP), Pimenta et al., supra; CEPU-1; GP55, Wilson et al., J. Cell Sci. 109: 3129-3138 (1996); Eur. J. Neurosci. 9(2): 334-41 (1997); and AvGp50, Hancox et al., Brain Res. Mol. Brain Res. 44(2): 273-85 (1997).

While the expression of neurotrimin appears to be widespread, it does appear to correlated with the development of several neural circuits. For example, between E18 and P10, neurotimin mRNA expression within the forebrain is maintained at high levels in neurons of the developing thalamus, cortical subplate, and cortex, particularly laminae V and VI (with less intense expression in II, II, and IV, and minimal expression in lamina I). Cortical subplate neurons may provide an early, temporary scaffold for the ingrowing thalamic afferents en route to their final synaptic targets in the cortex. Allendoerfer and Shatz, Annu. Rev. Neurosci. 17: 185-218 (1994). Conversely, subplate neurons have been suggested to be required for cortical neurons from layer V to select VI to grow into the thalamus, and neurons from layer V to select their targets in the colliculus, pons, and spinal cord (McConnell et al., J. Neurosci. 14: 1892-1907 (1994). The high level expression of neurotrimin in many of these projections suggests that it could be involved in their development.

In the hindbrain, high levels of neurotrimin message expression were observed within the pontine nucleus and by the internal granule cells and Purkinje cells of the cerebellum. The pontine nucleus received afferent input from a variety of sources including corticopontine fibers of layer V, and is a major source of afferent input, via mossy fibers, to the granule cells which, in turn, are a major source of afferent input via parallel fibers to Purkinje cells. [Palay and Chan-Palay, The cerebellar cortex: cytology and organization. New York: Springer (1974]. High level expression of neurotrimin these neurons again suggests potential involvement in the establishment of these circuits.

Neurotrimin also exhibits a graded expression pattern in the early postnatal striatum. Increased neurotrimin expression is found overlying the dorsolateral striatum of the rat, while lesser hybridization intensity is seen overlying the ventromedial striatum. Struyk et al., supra. This region of higher neurotrimin hybridization intensity does not correspond to a cytoarchitecturally differentiable region, rather it corresponds to the primary area of afferent input from layer VI of the contralateral sensorimotor cortex (Gerfen, Nature 311: 461-464 (1984); Donoghue and Herkenham, Brain Res. 365: 397-403 (1986)). The ventromedial striatum, by contrast, receives the majority of its afferent input from the perirhinal and association cortex. It is noteworthy that a complementary graded pattern of LAMP expression, has been observed within the striatium, with highest expression in ventromedial regions, and lowest expression dorsolaterally. Levitt, Science 223: 299-301 (1985); Chesselet et al., Neuroscience 40: 725-733 (1991).

87. PRO403

Type II transmembrane proteins, also known as single pass transmembrane proteins have an N-terminal portion lodged in the cytoplasm while the C-terminal portion is exposed to the extracellular domain.

Endothelin is a family of vasoconstrictor peptides about which much activity has been focused to better understand its basic pharmacological, biochemical and molecular biological features, including the presence and

structure of isopeptides and their genes (endothelin-1, -2 and û3), regulation of gene expression, intracellular processing, specific endothelin converting enzymes (ECE), receptor subtypes (ET-A and ET-B), intracellular signal transduction following receptor activation, etc.

The endothelin (ET) family of peptides have potent vascular, cardiac and renal actions which may be of pathophysiological importance in many human disease states. ET-1 is expressed as an inactive 212 amino acid prepropeptide. The prepropeptide is first cleaved at Arg52-Cys53 and Arg92-Ala93 and then the carboxy terminal Lys91 and Arg92 are trimmed from the protein to generate the propeptide big ET-1.

Endothelin is generated from inactive intermediates, the big endothelins, by a unique processing event catalyzed by the zinc metalloprotease, endothelin converting enzyme (ECE). ECE was recently cloned, and its structure was shown to be a single pass transmembrane protein with a short intracellular N-terminal and a long extracellular C-terminal that contains the catalytic domain and numerous N-glycosylation sites. ECEs cleave the endothelin propeptide between Trp73 and Val74 producing the active peptide, ET, which appears to function as a local rather than a circulating hormone (Rubanyi, G.M. & Polokoff, M.A., Pharmachological Reviews 46: 325-415 (1994). Thus ECE activity is a potential site of regulation of endothelin production and a possible target for therapeutic intervention in the endothelin system. By blocking ECE activity, it is possible stop the production of ET-1 by inhibiting the conversion of the relatively inactive precursor, big ET-1, to the physiologically active form.

Endothelins may play roles in the pathophysiology of a number of disease states including: 1) cardiovascular diseases (vasospasm, hypertension, myocardial ischemia; reperfusion injury and acute myochardial infarction, stroke (cerebral ischemia), congestive heart failure, shock, atherosclerosis, vascular thickening); 2) kidney disease (acute and chronic renal failure, glomerulonephritis, cirrhosis); 3) lung disease (bronchial asthma, pulmonary hypertension); 4) gastrointestinal disorders (gastric ulcer, inflammatory bowel diseases); 5) reproductive disorders (premature labor, dysmenorhea, preeclampsia) and 6) carcinogenesis. Rubanyi & Polokoff, supra.

SUMMARY OF THE INVENTION

1. PRO213

Applicants have identified a cDNA clone that encodes a novel polypeptide, wherein the polypeptide is designated in the present application as "PRO213".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO213 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO213 polypeptide having amino acid residues 1 to 295 of Figure 2 (SEQ ID NO:2), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another embodiment, the invention provides isolated PRO213 polypeptide. In particular, the invention provides isolated native sequence PRO213 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 295 of Figure 2 (SEQ ID NO:2).

2. PRO274

Applicants have identified a cDNA clone that encodes a novel polypeptide, wherein the polypeptide is designated in the present application as " PRO274".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO274 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO274 polypeptide having amino acid residues 1 to 492 of Figure 4 (SEQ ID NO:7), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA39987-1184 vector deposited on April 21, 1998 as ATCC 209786 which includes the nucleotide sequence encoding PRO274.

In another embodiment, the invention provides isolated PRO274 polypeptide. In particular, the invention provides isolated native sequence PRO274 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 492 of Figure 4 (SEQ ID NO:7). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO274 polypeptide. Optionally, the PRO274 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA39987-1184 vector deposited on April 21, 1998 as ATCC 209786.

In another embodiment, the invention provides three expressed sequence tags (EST) comprising the nucleotide sequences of SEQ ID NO:8 (herein designated as DNA17873), SEQ ID NO:9 (herein designated as DNA36157) and SEQ ID NO:10 (herein designated as DNA28929) (see Figure 5-7, respactively).

3. PRO300

Applicants have identified a cDNA clone that encodes a novel polypeptide, wherein the polypeptide is designated in the present application as "PRO300".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO300 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO300 polypeptide having amino acid residues 1 to 457 of Figure 9 (SEQ ID NO:19), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA40625-1189 vector deposited on April 21, 1998 as ATCC 209788 which includes the nucleotide sequence encoding PRO300.

In another embodiment, the invention provides isolated PRO300 polypeptide. In particular, the invention provides isolated native sequence PRO300 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 457 of Figure 9 (SEQ ID NO:19). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO300 polypeptide. Optionally, the PRO300 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of

the DNA40625-1189 vector deposited on April 21, 1998 as ATCC 209788.

4. PRO284

Applicants have identified a cDNA clone that encodes a novel transmembrane polypeptide, wherein the polypeptide is designated in the present application as "PRO284".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO284 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO284 polypeptide having amino acid residues 1 to 285 of Figure 11 (SEQ ID NO:28), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO284 polypeptide having amino acid residues about 25 to 285 of Figure 11 (SEQ ID NO:28) or 1 or about 25 to X of Figure 11 (SEQ ID NO:28), where X is any amino acid from 71 to 80 of Figure 11 (SEQ ID NO:28), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA23318-1211 vector deposited on April 21, 1998 as ATCC 209787 which includes the nucleotide sequence encoding PRO284.

In another embodiment, the invention provides isolated PRO284 polypeptide. In particular, the invention provides isolated native sequence PRO284 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 285 of Figure 11 (SEQ ID NO:28). Additional embodiments of the present invention are directed to isolated PRO284 polypeptides comprising amino acids about 25 to 285 of Figure 11 (SEQ ID NO:28) or 1 or about 25 to X of Figure 11 (SEQ ID NO:28), where X is any amino acid from 71 to 80 of Figure 11 (SEQ ID NO:28). Optionally, the PRO284 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA23318-1211 vector deposited on April 21, 1998 as ATCC 209787.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12982 which comprises the nucleotide sequence of SEQ ID NO:29.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA15886 which comprises the nucleotide sequence of SEQ ID NO:30.

5. PRO296

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the sarcoma-amplified protein SAS, wherein the polypeptide is designated in the present application as "PRO296".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO296 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO296 polypeptide having amino acid residues 1 to 204 of Figure 15 (SEQ ID NO:36), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO296

polypeptide having amino acid residues about 35 to 204 of Figure 15 (SEQ ID NO:36) or amino acid 1 or about 35 to X of Figure 15 (SEQ ID NO:36), where X is any amino acid from 42 to 51 of Figure 15 (SEQ ID NO:36), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA39979-1213 vector deposited on April 21, 1998 as ATCC 209789 which includes the nucleotide sequence encoding PRO296.

In another embodiment, the invention provides isolated PRO296 polypeptide. In particular, the invention provides isolated native sequence PRO296 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 204 of Figure 15 (SEQ ID NO:36). Additional embodiments of the present invention are directed to PRO296 polypeptides comprising amino acids about 35 to 204 of Figure 15 (SEQ ID NO:36) or amino acid 1 or about 35 to X of Figure 15 (SEQ ID NO:36), where X is any amino acid from 42 to 51 of Figure 15 (SEQ ID NO:36). Optionally, the PRO296 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA39979-1213 vector deposited on April 21, 1998 as ATCC 209789.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA23020 comprising the nucleotide sequence of SEQ ID NO:37.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA21971 comprising the nucleotide sequence of SEQ ID NO:38.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA29037 comprising the nucleotide sequence of SEQ ID NO:39.

6. PRO329

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to a high affinity immunoglobulin F_c receptor, wherein the polypeptide is designated in the present application as "PRO329".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO329 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO329 polypeptide having amino acid residues 1 to 359 of Figure 20 (SEQ ID NO:45), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA40594-1233 vector deposited on February 5, 1998 as ATCC 209617 which includes the nucleotide sequence encoding PRO329.

In another embodiment, the invention provides isolated PRO329 polypeptide. In particular, the invention provides isolated native sequence PRO329 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 359 of Figure 20 (SEQ ID NO:45). Optionally, the PRO329 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA40594-1233 vector deposited on February 5, 1998 as ATCC 209617.

7. PRO362

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to A33 antigen and HCAR membrane-bound protein, wherein the polypeptide is designated in the present application as "PRO362".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO362 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO362 polypeptide having amino acid residues 1 to 321 of Figure 22 (SEQ ID NO:52), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO362 polypeptide having amino acid residues 1 to X of Figure 22 (SEQ ID NO:52) where X is any amino acid from amino acid 271 to 280, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45416-1251 vector deposited on February 5, 1998 as ATCC 209620 which includes the nucleotide sequence encoding PRO362.

In another embodiment, the invention provides isolated PRO362 polypeptide. In particular, the invention provides isolated native sequence PRO362 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 321 of Figure 22 (SEQ ID NO:52). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO362 polypeptide comprising amino acids 1 to X of the amino acid sequence shown in Figure 22 (SEQ ID NO:52), wherein X is any amino acid from amino acid 271 to 280. Optionally, the PRO362 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45416-1251 vector deposited on February 5, 1998 as ATCC 209620.

8. PRO363

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the cell surface receptor protein HCAR, wherein the polypeptide is designated in the present application as "PRO363".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO363 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO363 polypeptide having amino acid residues 1 to 373 of Figure 24 (SEQ ID NO:59), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding a PRO363 extracellular domain polypeptide having amino acid residues 1 to X of Figure 24 (SEQ ID NO:59) where X is any amino acid from amino acid 216 to amino acid 225, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45419-1252 vector deposited on February 5, 1998 as ATCC 209616 which includes the nucleotide sequence encoding PRO363.

In another embodiment, the invention provides isolated PRO363 polypeptide. In particular, the

invention provides isolated native sequence PRO363 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 373 of Figure 24 (SEQ ID NO:59). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO363 polypeptide, wherein that extracellular domain may comprise amino acids 1 to X of the sequence shown in Figure 24 (SEQ ID NO:59), where X is any amino acid from amino acid 216 to 225. Optionally, the PRO363 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45419-1252 vector deposited on February 5, 1998 as ATCC 209616.

9. PRO868

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to tumor necrosis factor receptor, wherein the polypeptide is designated in the present application as "PRO868".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO868 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO868 polypeptide having amino acid residues 1 to 655 of Figure 26 (SEQ ID NO:64), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO868 polypeptide having amino acid residues 1 to X of Figure 26 (SEQ ID NO:64), where X is any amino acid from amino acid 343 to 352 of the sequence shown in Figure 26 (SEQ ID NO:64), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In yet another aspect, the isolated nucleic acid comprises DNA encoding the PRO868 polypeptide having amino acid residues X to 655 of Figure 26 (SEQ ID NO:64), where X is any amino acid from amino acid 371 to 380 of the sequence shown in Figure 26 (SEQ ID NO:64), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA52594-1270 vector deposited on March 17, 1998 as ATCC 209679 which includes the nucleotide sequence encoding PRO868.

In another embodiment, the invention provides isolated PRO868 polypeptide. In particular, the invention provides isolated native sequence PRO868 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 655 of Figure 26 (SEQ ID NO:64). In another aspect, the isolated PRO868 polypeptide comprises amino acid residues 1 to X of Figure 26 (SEQ ID NO:64), where X is any amino acid from amino acid 343 to 352 of the sequence shown in Figure 26 (SEQ ID NO:64). In yet another aspect, the PRO868 polypeptide comprises amino acid residues X to 655 of Figure 26 (SEQ ID NO:64), where X is any amino acid from amino acid 371 to 380 of the sequence shown in Figure 26 (SEQ ID NO:64). Optionally, the PRO868 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA52594-1270 vector deposited on March 17, 1998 as ATCC 209679.

10. PRO382

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to serine proteases, wherein the polypeptide is designated in the present application as "PRO382".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO382 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO382 polypeptide having amino acid residues 1 to 453 of Figure 28 (SEQ ID NO:69), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45234-1277 vector deposited on March 5, 1998 as ATCC 209654 which includes the nucleotide sequence encoding PRO382.

In another embodiment, the invention provides isolated PRO382 polypeptide. In particular, the invention provides isolated native sequence PRO382 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 453 of Figure 28 (SEQ ID NO:69). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO382 polypeptide, with or without the signal peptide. Optionally, the PRO382 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45234-1277 vector deposited on March 5, 1998 as ATCC 209654.

11. PRO545

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to meltrin, wherein the polypeptide is designated in the present application as "PRO545".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO545 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO545 polypeptide having amino acid residues 1 to 735 of Figure 30 (SEQ ID NO:74), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 5, 1998 as ATCC 209655 which includes the nucleotide sequence encoding PRO545.

In another embodiment, the invention provides isolated PRO545 polypeptide. In particular, the invention provides isolated native sequence PRO545 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 735 of Figure 30 (SEQ ID NO:74). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO545 polypeptide. Optionally, the PRO545 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 5, 1998 as ATCC 209655.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13217 comprising the nucleotide sequence of SEQ ID NO:75 (Figure 31).

12. PRO617

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CD24,

wherein the polypeptide is designated in the present application as "PRO617".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO617 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO617 polypeptide having amino acid residues 1 to 67 of Figure 33 (SEQ ID NO:85), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48309-1280 vector deposited on March 5, 1998 as ATCC 209656 which includes the nucleotide sequence encoding PRO617.

In another embodiment, the invention provides isolated PRO617 polypeptide. In particular, the invention provides isolated native sequence PRO617 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 67 of Figure 33 (SEQ ID NO:85). Optionally, the PRO617 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48309-1280 vector deposited on March 5, 1998 as ATCC 209656.

13. PRO700

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to protein disulfide isomerase, wherein the polypeptide is designated in the present application as "PRO700".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO700 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO700 polypeptide having amino acid residues 1 to 432 of Figure 35 (SEQ ID NO:90), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO700 polypeptide having amino acid residues from about 34 to 432 of Figure 35 (SEQ ID NO:90), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 31, 1998 as ATCC 209721 which includes the nucleotide sequence encoding PRO700.

In another embodiment, the invention provides isolated PRO700 polypeptide. In particular, the invention provides isolated native sequence PRO700 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 432 of Figure 35 (SEQ ID NO:90). In another embodiment, the invention provides an isolated PRO700 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 34 to 432 of Figure 35 (SEQ ID NO:90). Optionally, the PRO700 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 31, 1998 as ATCC 209721.

14. PRO702

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to

conglutinin, wherein the polypeptide is designated in the present application as "PRO702".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO702 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO702 polypeptide having amino acid residues 1 to 277 of Figure 37 (SEQ ID NO:97), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO702 polypeptide having amino acid residues 26 to 277 of Figure 37 (SEQ ID NO:97), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA50980-1286 vector deposited on March 31, 1998 as ATCC 209717 which includes the nucleotide sequence encoding PRO702.

In another embodiment, the invention provides isolated PRO702 polypeptide. In particular, the invention provides isolated native sequence PRO702 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 277 of Figure 37 (SEQ ID NO:97). An additional embodiment of the present invention is directed to an isolated PRO702 polypeptide comprising amino acid residues 26 to 277 of Figure 37 (SEQ ID NO:97). Optionally, the PRO702 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA50980-1286 vector deposited on March 31, 1998 as ATCC 209717.

15. PRO703

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to VLCAS, wherein the polypeptide is designated in the present application as "PRO703".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO703 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO703 polypeptide having amino acid residues 1 to 730 of Figure 39 (SEQ ID NO:102), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO703 polypeptide having amino acid residues from about 43 to 730 of Figure 39 (SEQ ID NO:102), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA50913-1287 vector deposited on March 31, 1998 as ATCC 209716 which includes the nucleotide sequence encoding PRO703.

In another embodiment, the invention provides isolated PRO703 polypeptide. In particular, the invention provides isolated native sequence PRO703 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 730 of Figure 39 (SEQ ID NO:102). In another embodiment, the invention provides an isolated PRO703 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 43 to 730 of Figure 30 (SEQ ID NO:102). Optionally, the PRO730

polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA50913-1287 vector deposited on March 31, 1998 as ATCC 209716.

16. PRO705

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to K-glypican, wherein the polypeptide is designated in the present application as "PRO705".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO705 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO705 polypeptide having amino acid residues 1 to 555 of Figure 41 (SEQ ID NO:109), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO705 polypeptide having amino acid residues about 24 to 555 of Figure 41 (SEQ ID NO:109), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA50914-1289 vector deposited on March 31, 1998 as ATCC 209722 which includes the nucleotide sequence encoding PRO705.

In another embodiment, the invention provides isolated PRO705 polypeptide. In particular, the invention provides isolated native sequence PRO705 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 555 of Figure 41 (SEQ ID NO:109). An additional embodiment of the present invention is directed to an isolated PRO705 polypeptide comprising amino acid residues about 24 to 555 of Figure 41 (SEQ ID NO:109). Optionally, the PRO705 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA50914-1289 vector deposited on March 31, 1998 as ATCC 209722.

17. PRO708

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the aryl sulfatases, wherein the polypeptide is designated in the present application as "PRO708".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO708 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO708 polypeptide having amino acid residues 1 to 515 of Figure 43 (SEQ ID NO:114), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48296-1292 vector deposited on March 11, 1998 as ATCC 209668 which includes the nucleotide sequence encoding PRO708.

In another embodiment, the invention provides isolated PRO708 polypeptide. In particular, the invention provides isolated native sequence PRO708 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 515 of Figure 43 (SEQ ID NO:114). Another embodiment is directed

to a PRO708 polypeptide comprising residues 38-515 of the amino acid sequence shown in Figure 43 (SEQ ID NO:114). Optionally, the PRO708 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48296-1292 vector deposited on March 11, 1998 as ATCC 209668.

18. PRO320

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to fibulin, wherein the polypeptide is designated in the present application as "PRO320".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO320 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO320 polypeptide having amino acid residues 1 to 338 of Figure 45 (SEQ ID NO:119), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 11, 1998 as ATCC 209670 which includes the nucleotide sequence encoding PRO320.

In another embodiment, the invention provides isolated PRO320 polypeptide. In particular, the invention provides isolated native sequence PRO320 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 338 of Figure 45 (SEQ ID NO:119). Optionally, the PRO320 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 11, 1998 as ATCC 209670.

19. PRO324

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to oxidoreductases, wherein the polypeptide is designated in the present application as "PRO324".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO324 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO324 polypeptide having amino acid residues 1 to 289 of Figure 47 (SEQ ID NO:124), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO324 polypeptide having amino acid residues 1 or about 32 to X of Figure 47 (SEQ ID NO:124), where X is any amino acid from 131 to 140, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA36343-1310 vector deposited on March 30, 1998 as ATCC 209718 which includes the nucleotide sequence encoding PRO324.

In another embodiment, the invention provides isolated PRO324 polypeptide. In particular, the invention provides isolated native sequence PRO324 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 289 of Figure 47 (SEQ ID NO:124). The invention also provides isolated PRO324 polypeptide comprising residues 1 or about 32 to X of Figure 47 (SEQ ID NO:124), wherein X is any amino acid from about 131-140. Optionally, the PRO324 polypeptide is obtained or is obtainable by expressing

the polypeptide encoded by the cDNA insert of the DNA36343-1310 vector deposited on March 30, 1998 as ATCC 209718.

20. PRO351

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to prostasin, wherein the polypeptide is designated in the present application as "PRO351".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO351 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO351 polypeptide having amino acid residues 1 to 571 of Figure 49 (SEQ ID NO:132), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO351 polypeptide having amino acid residues about 16 to 571 of Figure 49 (SEQ ID NO:132), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA40571-1315 vector deposited on April 21, 1998 as ATCC 209784 which includes the nucleotide sequence encoding PRO351.

In another embodiment, the invention provides isolated PRO351 polypeptide. In particular, the invention provides isolated native sequence PRO351 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 571 of Figure 49 (SEQ ID NO:132). In another embodiment, the invention provides an isolated PRO351 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 16 to 571 of Figure 49 (SEQ ID NO:132). Optionally, the PRO351 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA40571-1315 vector deposited on April 21, 1998 as ATCC 209784.

21. PRO352

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to butyrophilin, wherein the polypeptide is designated in the present application as "PRO352".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO352 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO352 polypeptide having amino acid residues 1 to 316 of Figure 51 (SEQ ID NO:137), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO352 polypeptide having amino acid residues of about 29 to 316 of Figure 51 (SEQ ID NO:137), or 1 or about 29 to X of Figure 51, where X is any amino acid from 246 to 255, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA41386-1316 vector deposited on March 26, 1998 as ATCC 209703 which includes the nucleotide sequence encoding PRO352.

In another embodiment, the invention provides isolated PRO352 polypeptide. In particular, the invention provides isolated native sequence PRO352 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 316 of Figure 51 (SEQ ID NO:137). In other embodiments, the invention provides isolated PRO352 polypeptide comprising residues about 29 to 316 of Figure 51 (SEQ ID NO:137) and 1 or about 29 to X of Figure 51 (SEQ ID NO:137), wherein X is any amino acid from 246 to 255. Optionally, the PRO352 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA41386-1316 vector deposited on March 26, 1998 as ATCC 209703.

22. PRO381

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to immunophilin proteins, wherein the polypeptide is designated in the present application as "PRO381".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO381 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO381 polypeptide having amino acid residues 1 to 211 of Figure 53 (SEQ ID NO:145), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO381 polypeptide having amino acid residues about 21 to 211 of Figure 53 (SEQ ID NO:145), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44194-1317 vector deposited on April 28, 1998 as ATCC 209808 which includes the nucleotide sequence encoding PRO381.

In another embodiment, the invention provides isolated PRO381 polypeptide. In particular, the invention provides isolated native sequence PRO381 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 211 of Figure 53 (SEQ ID NO:145). Another embodiment is directed to a PRO381 plypeptide comprising amino acids about 21 to 211 of Figure 53 (SEQ ID NO:145). Optionally, the PRO381 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44194-1317 vector deposited on April 28, 1998 as ATCC 209808.

23. PRO386

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the beta-2 subunit of a sodium channel, wherein the polypeptide is designated in the present application as "PRO386".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO386 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO386 polypeptide having amino acid residues 1 to 215 of Figure 55 (SEQ ID NO:150), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO386 polypeptide having amino acid residues about 21 to 215 of Figure 55 (SEQ ID NO:150) or 1 or about 21 to X,

where X is any amino acid from 156 to 165 of Figure 55 (SEQ ID NO:150), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45415-1318 vector deposited on April 28, 1998 as ATCC 209810 which includes the nucleotide sequence encoding PRO386.

In another embodiment, the invention provides isolated PRO386 polypeptide. In particular, the invention provides isolated native sequence PRO386 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 215 of Figure 55 (SEQ ID NO:150). Other embodiments of the present invention are directed to PRO386 polypeptides comprising amino acids about 21 to 215 of Figure 55 (SEQ ID NO:150) and 1 or about 21 to X of Figure 55 (SEQ ID NO:150), wherein X is any amino acid from 156 to 165 of Figure 55 (SEQ ID NO:150). Optionally, the PRO386 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45415-1318 vector deposited on April 28, 1998 as ATCC 209810.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of SEQ ID NO:151 which corrsponds to an EST designated herein as DNA23350.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of SEQ ID NO:152 which corrsponds to an EST designated herein as DNA23536.

24. PRO540

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to LCAT, wherein the polypeptide is designated in the present application as "PRO540".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO540 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO540 polypeptide having amino acid residues 1 to 412 of Figure 59 (SEQ ID NO:157), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO540 polypeptide having amino acid residues about 29 to 412 of Figure 59 (SEQ ID NO:157), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44189-1322 vector deposited on March 26, 1998 as ATCC 209699 which includes the nucleotide sequence encoding PRO540.

In another embodiment, the invention provides isolated PRO540 polypeptide. In particular, the invention provides isolated native sequence PRO540 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 412 of Figure 59 (SEQ ID NO:157). The invention also provides isolated PRO540 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues about 29 to 412 of Figure 59 (SEQ ID NO:157). Optionally, the PRO540 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44189-1322 vector deposited

on March 26, 1998 as ATCC 209699.

25. PRO615

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to synaptogyrin, wherein the polypeptide is designated in the present application as "PRO615".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO615 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO615 polypeptide having amino acid residues 1 to 224 of Figure 61 (SEQ ID NO:162), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO615 polypeptide having amino acid residues X to 224 of Figure 61 (SEQ ID NO:162), where X is any amino acid from 157 to 166, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48304-1323 vector deposited on April 28, 1998 as ATCC 209811 which includes the nucleotide sequence encoding PRO615.

In another embodiment, the invention provides isolated PRO615 polypeptide. In particular, the invention provides isolated native sequence PRO615 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 224 of Figure 61 (SEQ ID NO:162). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO615 polypeptide which comprises amino acid residues X to 224 of Figure 61 (SEQ ID NO:162), where X is any amino acid from 157 to 166 of Figure 61 (SEQ ID NO:162). Optionally, the PRO615 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48304-1323 vector deposited on April 28, 1998 as ATCC 209811.

26. PRO618

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to enteropeptidase, wherein the polypeptide is designated in the present application as "PRO618".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO618 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO618 polypeptide having amino acid residues 1 to 802 of Figure 63 (SEQ ID NO:169), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding an isolated extracellular domain of a PRO618 polypeptide having amino acid residues X to 802 of Figure 63 (SEQ ID NO:169), where X is any amino acid from 63 to 72 of Figure 63 (SEQ ID NO:169), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49152-1324 vector deposited on April 28, 1998 as ATCC 209813 which includes the nucleotide sequence

encoding PRO618.

In another embodiment, the invention provides isolated PRO618 polypeptide. In particular, the invention provides isolated native sequence PRO618 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 802 of Figure 63 (SEQ ID NO:169). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO618 polypeptide comprising amino acid X to 802 where X is any amino acid from 63 to 72 of Figure 63 (SEQ ID NO:169). Optionally, the PRO618 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49152-1324 vector deposited on April 28, 1998 as ATCC 209813.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of SEQ ID NO:170, designated herein as DNA35597 (see Figure 64).

27. PRO719

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to lipoprotein lipase H, wherein the polypeptide is designated in the present application as "PRO719".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO719 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO719 polypeptide having amino acid residues 1 to 354 of Figure 66 (SEQ ID NO:178), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO719 polypeptide having amino acid residues about 17 to 354 of Figure 66 (SEQ ID NO:178), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49646-1327 vector deposited on March 26, 1998 as ATCC 209705 which includes the nucleotide sequence encoding PRO719.

In another embodiment, the invention provides isolated PRO719 polypeptide. In particular, the invention provides isolated native sequence PRO719 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 354 of Figure 66 (SEQ ID NO:178). In another embodiment, the invention provides isolated PRO719 polypeptide which comprises residues about 17 to 354 of Figure 66 (SEQ ID NO:178). Optionally, the PRO719 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49646-1327 vector deposited on March 26, 1998 as ATCC 209705.

28. PRO724

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the LDL receptor, wherein the polypeptide is designated in the present application as "PRO724".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO724 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO724 polypeptide having amino acid residues 1 to 713 of Figure 68 (SEQ ID NO:183), or is complementary to such

encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding a soluble PRO724 polypeptide having amino acid residues 1 to X of Figure 68 (SEQ ID NO:183) where X is any amino acid from amino acid 437 to 446, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The above two polypeptides may either possess or not possess the signal peptide. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49631-1328 vector deposited on April 28, 1998 as ATCC 209806 which includes the nucleotide sequence encoding PRO724.

In another embodiment, the invention provides isolated PRO724 polypeptide. In particular, the invention provides isolated native sequence PRO724 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 713 of Figure 68 (SEQ ID NO:183). In another embodiment, the invention provides isolated soluble PRO724 polypeptide. In particular, the invention provides isolated soluble PRO724 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to X of Figure 68 (SEQ ID NO:183), where X is any amino acid from 437 to 446 of the sequence shown in Figure 68 (SEQ ID NO:183). Optionally, the PRO724 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49631-1328 vector deposited on April 28, 1998 as ATCC 209806.

29. PRO772

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to A4 protein, wherein the polypeptide is designated in the present application as "PRO772".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO772 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO772 polypeptide having amino acid residues 1 to 152 of Figure 70 (SEQ ID NO:190), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO772 polypeptide having amino acid residues 1 to X of Figure 70 (SEQ ID NO:190), where X is any amino acid from 21 to 30 of Figure 70 (SEQ ID NO:190), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49645-1347 vector deposited on April 28, 1998 as ATCC 209809 which includes the nucleotide sequence encoding PRO772.

In another embodiment, the invention provides isolated PRO772 polypeptide. In particular, the invention provides isolated native sequence PRO772 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 152 of Figure 70 (SEQ ID NO:190). Additional embodiments of the present invention are directed to PRO772 polypeptides comprising amino acids 1 to X of Figure 70 (SEQ ID NO:190), where X is any amino acid from 21 to 30 of Figure 70 (SEQ ID NO:190). Optionally, the PRO772 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the

DNA49645-1347 vector deposited on April 28, 1998 as ATCC 209809.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA43509 comprising the nucleotide sequence of SEQ ID NO:191 (Figure 71).

30. PRO852

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to various protease enzymes, wherein the polypeptide is designated in the present application as "PRO852".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO852 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO852 polypeptide having amino acid residues 1 to 518 of Figure 73 (SEQ ID NO:196), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO852 polypeptide having amino acid residues about 21 to 518 of Figure 73 (SEQ ID NO:196) or 1 or about 21 to X of Figure 73 (SEQ ID NO:196) where X is any amino acid from amino acid 461 to amino acid 470 of Figure 73 (SEQ ID NO:196), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45493-1349 vector deposited on April 28, 1998 as ATCC 209805 which includes the nucleotide sequence encoding PRO852.

In another embodiment, the invention provides isolated PRO852 polypeptide. In particular, the invention provides isolated native sequence PRO852 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 518 of Figure 73 (SEQ ID NO:196). In other embodiments, the PRO852 comprises amino acids about 21 to amino acid 518 of Figure 73 (SEQ ID NO:196) or amino acids 1 or about 21 to X of Figure 73 (SEQ ID NO:196), where X is any amino acid from amino acid 461 to amino acid 470 of Figure 73 (SEQ ID NO:196). Optionally, the PRO852 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45493-1349 vector deposited on April 28, 1998 as ATCC 209805.

31. PRO853

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to reductase, wherein the polypeptide is designated in the present application as "PRO853".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO853 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO853 polypeptide having amino acid residues 1 to 377 of Figure 75 (SEQ ID NO:206), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO853 polypeptide having amino acid residues about 17 to 377 of Figure 75 (SEQ ID NO:206), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally,

under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48227-1350 vector deposited on April 28, 1998 as ATCC 209812 which includes the nucleotide sequence encoding PRO853.

In another embodiment, the invention provides isolated PRO853 polypeptide. In particular, the invention provides isolated native sequence PRO853 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 377 of Figure 75 (SEQ ID NO:206). In another embodiment, the invention provides an isolated PRO853 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 17 to 377 of Figure 75 (SEQ ID NO:206). Optionally, the PRO853 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48227-1350 vector deposited on April 28, 1998 as ATCC 209812.

32. PRO860

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to neurofascin, wherein the polypeptide is designated in the present application as "PRO860".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO860 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO860 polypeptide having amino acid residues 1 to 985 of Figure 77 (SEQ ID NO:211), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO860 polypeptide having amino acid residues 1 to X of Figure 77 (SEQ ID NO:211), where X is any amino acid from 443-452 of Figure 77 (SEQ ID NO:211), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA41404-1352 vector deposited on May 6, 1998 as ATCC 209844 which includes the nucleotide sequence encoding PRO860.

In another embodiment, the invention provides isolated PRO860 polypeptide. In particular, the invention provides isolated native sequence PRO860 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 985 of Figure 77 (SEQ ID NO:211). In another embodiment, the invention provides an isolated PRO860 polypeptide which includes an amino acid sequence comprising residues 1 to X of Figure 77 (SEQ ID NO:211), where X is any amino acid residue from 443 to 452 of Figure 77 (SEQ ID NO:211). Optionally, the PRO860 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA41404-1352 vector deposited on May 6, 1998 as ATCC 209844.

33. PRO846

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to CMRF35, wherein the polypeptide is designated in the present application as "PRO846".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO846 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO846

polypeptide having amino acid residues 1 to 332 of Figure 79 (SEQ ID NO:216), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO846 polypeptide having amino acid residues about 18 to 332 of Figure 79 (SEQ ID NO:216) or 1 or about 18 to X of SEQ ID NO:216, where X is any amino acid from 243 to 252 of Figure 79 (SEQ ID NO:216), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44196-1353 vector deposited on May 6, 1998 as ATCC 209847 which includes the nucleotide sequence encoding PRO846.

In another embodiment, the invention provides isolated PRO846 polypeptide. In particular, the invention provides isolated native sequence PRO846 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 332 of Figure 79 (SEQ ID NO:216). In other embodiments, the invention provides an isolated PRO846 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 18 to 332 of Figure 79 (SEQ ID NO:216). Additional embodiments of the present invention are directed to an isolated PRO846 polypeptide comprising amino acid 1 or about 18 to X of Figure 79 (SEQ ID NO:216), where X is any amino acid from 243 to 252 of Figure 79 (SEQ ID NO:216). Optionally, the PRO846 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44196-1353 vector deposited on May 6, 1998 as ATCC 209847.

34. <u>PRO862</u>

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to lysozyme, wherein the polypeptide is designated in the present application as "PRO862".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO862 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO862 polypeptide having amino acid residues 1 to 146 of Figure 81 (SEQ ID NO:221), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO862 polypeptide having amino acid residues about 19 to 146 of Figure 81 (SEQ ID NO:221), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA52187-1354 vector deposited on May 6, 1998 as ATCC 209845 which includes the nucleotide sequence encoding PRO862.

In another embodiment, the invention provides isolated PRO862 polypeptide. In particular, the invention provides isolated native sequence PRO862 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 146 of Figure 81 (SEQ ID NO:221). In another embodiment, the invention provides an isolated PRO862 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 19 to 146 of Figure 81 (SEQ ID NO:221). Optionally, the PRO862

polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA52187-1354 vector deposited on May 6, 1998 as ATCC 209845.

35. PRO864

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence similarity to Wnt-4, wherein the polypeptide is designated in the present application as "PRO864".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO864 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO864 polypeptide having amino acid residues 1 to 351 of Figure 83 (SEQ ID NO:226), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO864 polypeptide having amino acid residues about 23 to 351 of Figure 83 (SEQ ID NO:226), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48328-1355 vector deposited on May 6, 1998 as ATCC 209843 which includes the nucleotide sequence encoding PRO864.

In another embodiment, the invention provides isolated PRO864 polypeptide. In particular, the invention provides isolated native sequence PRO864 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 351 of Figure 83 (SEQ ID NO:226). In another embodiment, the invention provides an isolated PRO864 polypeptide absent the signal sequence, which includes an amino acid sequence comprising residues from about 23 to 351 of Figure 83 (SEQ ID NO:226). Optionally, the PRO864 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48328-1355 vector deposited on May 6, 1998 as ATCC 209843 .

36. PRO792

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CD23, wherein the polypeptide is designated in the present application as "PRO792".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO792 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO792 polypeptide having amino acid residues 1 to 293 of Figure 85 (SEQ ID NO:231), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO792 polypeptide having amino acid residues X to 293 of Figure 85 (SEQ ID NO:231) where X is any amino acid from 50 to 59 of Figure 85 (SEQ ID NO:231), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA56352-1358 vector deposited on May 6, 1998 as ATCC 209846 which includes the nucleotide sequence encoding PRO792.

In another embodiment, the invention provides isolated PRO792 polypeptide. In particular, the invention provides isolated native sequence PRO792 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 293 of Figure 85 (SEQ ID NO:231). An additional embodiment of the present invention is directed to PRO792 polypeptide comprising amino acids X to 293 of Figure 85 (SEQ ID NO:231), where X is any amino acid from 50 to 59 of Figure 85 (SEQ ID NO:231). Optionally, the PRO792 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA56352-1358 vector deposited on May 6, 1998 as ATCC 209846.

37. PRO866

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to mindin and spondin proteins, wherein the polypeptide is designated in the present application as "PRO866".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO866 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO866 polypeptide having amino acid residues 1 to 331 of Figure 87 (SEQ ID NO:236), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In another aspect, the isolated nucleic acid comprises DNA encoding the PRO866 polypeptide having amino acid residues about 27 to 229 of Figure 87 (SEQ ID NO:236), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA53971-1359 vector deposited on April 7, 1998 as ATCC 209750 which includes the nucleotide sequence encoding PRO866.

In another embodiment, the invention provides isolated PRO866 polypeptide. In particular, the invention provides isolated native sequence PRO866 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 331 of Figure 87 (SEQ ID NO:236). Another embodiment of the present invention is directed to PRO866 polypeptides comprising amino acids about 27 to 331 of Figure 87 (SEQ ID NO:236). Optionally, the PRO866 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA53971-1359 vector deposited on April 7, 1998 as ATCC 209750.

38. PRO871

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CyP-60, wherein the polypeptide is designated in the present application as "PRO871".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO871 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO871 polypeptide having amino acid residues 1 to 472 of Figure 89 (SEQ ID NO:245), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO871 polypeptide having amino acid residues about 22 to 472 of Figure 89 (SEQ ID NO:245), or is complementary

to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA50919-1361 vector deposited on May 6, 1998 as ATCC 209848 which includes the nucleotide sequence encoding PRO871.

In another embodiment, the invention provides isolated PRO871 polypeptide. In particular, the invention provides isolated native sequence PRO871 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 472 of Figure 89 (SEQ ID NO:245). An additional embodiment of the present invention is directed to PRO871 polypeptides comprising amino acids about 22 to 472 of Figure 89 (SEQ ID NO:245). Optionally, the PRO871 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA50919-1361 vector deposited on May 6, 1998 as ATCC 209848.

39. PRO873

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to carboxylesterase, wherein the polypeptide is designated in the present application as "PRO873".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO873 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO873 polypeptide having amino acid residues 1 to 545 of Figure 91 (SEQ ID NO:254), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO873 polypeptide having amino acid residues about 30 to about 545 of Figure 91 (SEQ ID NO:254), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44179-1362 vector deposited on May 6, 1998 as ATCC 209851 which includes the nucleotide sequence encoding PRO873.

In another embodiment, the invention provides isolated PRO873 polypeptide. In particular, the invention provides isolated native sequence PRO873 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 545 of Figure 91 (SEQ ID NO:254). Additional embodiments of the present invention are directed to PRO873 polypeptides comprising amino acids about 30 to about 545 of Figure 91 (SEQ ID NO:254). Optionally, the PRO873 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44179-1362 vector deposited on May 6, 1998 as ATCC 209851.

40. PRO940

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CD33 and OB binding protein-2, wherein the polypeptide is designated in the present application as "PRO940".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO940 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO940

polypeptide having amino acid residues 1 to 544 of Figure 93 (SEQ ID NO:259), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO940 polypeptide having amino acid residues about 16 to 544 of Figure 93 (SEQ ID NO:259) or 1 or about 16 to X of Figure 93 (SEQ ID NO:259), where X is any amino acid from 394 to 403 of Figure 93 (SEQ ID NO:259), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA54002-1367 vector deposited on April 7, 1998 as ATCC 209754 which includes the nucleotide sequence encoding PRO940.

In another embodiment, the invention provides isolated PRO940 polypeptide. In particular, the invention provides isolated native sequence PRO940 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 544 of Figure 93 (SEQ ID NO:259). Other embodiments of the present invention are directed to PRO940 polypeptides comprising amino acids about 16 to 544 of Figure 93 (SEQ ID NO:259) or 1 or about 16 to X of Figure 93 (SEQ ID NO:259), where X is any amino acid from 394 to 403 of Figure 93 (SEQ ID NO:259). Optionally, the PRO940 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA54002-1367 vector deposited on April 7, 1998 as ATCC 209754.

41. PRO941

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to a cadherin protein, wherein the polypeptide is designated in the present application as "PRO941".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO941 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO941 polypeptide having amino acid residues 1 to 772 of Figure 95 (SEQ ID NO:264), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO941 polypeptide having amino acid residues about 22 to 772 of Figure 95 (SEQ ID NO:264) or 1 or about 22 to X of Figure 95 (SEQ ID NO:264), where X is any amino acid from 592 to 601 of Figure 95 (SEQ ID NO:264), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA53906-1368 vector deposited on April 7, 1998 as ATCC 209747 which includes the nucleotide sequence encoding PRO941.

In another embodiment, the invention provides isolated PRO941 polypeptide. In particular, the invention provides isolated native sequence PRO941 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 772 of Figure 95 (SEQ ID NO:264). Additional embodiments of the present invention are directed to PRO941 polypeptides which comprise amino acid about 21 to 772 of Figure 95 (SEQ ID NO:264) or 1 or about 22 to X of Figure 95 (SEQ ID NO:264), where X is any amino acid from

592 to 601 of Figure 95 (SEQ ID NO:264). Optionally, the PRO941 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA53906-1368 vector deposited on April 7, 1998 as ATCC 209747.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA6415 comprising the nucleotide sequence of Figure 96 (SEQ ID NO:265).

42. **PRO944**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to Clostridium perfringens enterotoxin receptor (CPE-R), wherein the polypeptide is designated in the present application as "PRO944".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO944 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO944 polypeptide having amino acid residues 1 to 211 of Figure 98 (SEQ ID NO:270), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO944 polypeptide having amino acid residues about 22 to 229 of Figure 98 (SEQ ID NO:270) or amino acid 1 or about 22 to X of Figure 98 (SEQ ID NO:270) where X is any amino acid from 77 to 80 of Figure 98 (SEQ ID NO:270), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA52185-1370 vector deposited on May 14, 1998 as ATCC 209861 which includes the nucleotide sequence encoding PRO944.

In another embodiment, the invention provides isolated PRO944 polypeptide. In particular, the invention provides isolated native sequence PRO944 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 211 of Figure 98 (SEQ ID NO:270). Additional embodiments of the present invention are directed to PRO944 polypeptides comprising amino acids about 22 to 211 of Figure 98 (SEQ ID NO:270) or amino acid 1 or about 22 to X of Figure 98 (SEQ ID NO:270), where X is any amino acid from 77 to 86 of Figure 98 (SEQ ID NO:270). Optionally, the PRO944 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA52185-1370 vector deposited on May 14, 1998 as ATCC 209861.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA14007 comprising the nucleotide sequence of Figure 99 (SEQ ID NO:271).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12733 comprising the nucleotide sequence of Figure 100 (SEQ ID NO:272).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12746 comprising the nucleotide sequence of Figure 101 (SEQ ID NO:273).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12834 comprising the nucleotide sequence of Figure 102 (SEQ ID NO:274).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12846 comprising the nucleotide sequence of Fiugure 103 (SEQ ID NO:275).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13104 comprising the nucleotide sequence of Figure 104 (SEQ ID NO:276).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13259 comprising the nucleotide sequence of Figure 105 (SEQ ID NO:277).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13959 comprising the nucleotide sequence of Figure 106 (SEQ ID NO:278).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13961 comprising the nucleotide sequence of Figure 107 (SEQ ID NO:279).

43. PRO983

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to a vesicle associated protein, VAP-33, wherein the polypeptide is designated in the present application as "PRO983".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO983 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO983 polypeptide having amino acid residues 1 to 243 of Figure 109 (SEQ ID NO:284), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO983 polypeptide having amino acid residue 1 to X of Figure 109 (SEQ ID NO:284) where X is any amino acid from 219 to 228 of Figure 109 (SEQ ID NO:284), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA53977-1371 vector deposited on May 14, 1998 as ATCC 209862 which includes the nucleotide sequence encoding PRO983.

In another embodiment, the invention provides isolated PRO983 polypeptide. In particular, the invention provides isolated native sequence PRO983 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 243 of Figure 109 (SEQ ID NO:284). Additional embodiments of the present invention are directed to PRO983 polypeptides comprising amino acid 1 to X of Figure 109 (SEQ ID NO:284), where X is any amino acid from 219 to 228 of Figure 109 (SEQ ID NO:284). Optionally, the PRO983 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA53977-1371 vector deposited on May 14, 1998 as ATCC 209862.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA17130 comprising the nucleotide sequence of Figure 110 (SEQ ID NO:285).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA23466 comprising the nucleotide sequence of Figure 111 (SEQ ID NO:286).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA26818 comprising the nucleotide sequence of Figure 112 (SEQ ID NO:287).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA37618 comprising the nucleotide sequence of Figure 113 (SEQ ID NO:288).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA41732 comprising the nucleotide sequence of Figure 114 (SEQ ID NO:289).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA45980 comprising the nucleotide sequence of Figure 115 (SEQ ID NO:290).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA46372 comprising the nucleotide sequence of Figure 116 (SEQ ID NO:291).

44. PRO1057

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to proteases, wherein the polypeptide is designated in the present application as "PRO1057".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1057 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1057 polypeptide having amino acid residues 1 to 413 of Figure 118 (SEQ ID NO:296), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1057 polypeptide having amino acid residues about 17 to 413 of Figure 118 (SEQ ID NO:296), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA57253-1382 vector deposited on May 14, 1998 as ATCC 209867 which includes the nucleotide sequence encoding PRO1057.

In another embodiment, the invention provides isolated PRO1057 polypeptide. In particular, the invention provides isolated native sequence PRO1057 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 413 of Figure 118 (SEQ ID NO:296). Additional embodiments of the present invention are directed to PRO1057 polypeptides comprising amino acids about 17 to 413 of Figure 118 (SEQ ID NO:296). Optionally, the PRO1057 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA57253-1382 vector deposited on May 14, 1998 as ATCC 209867.

45. PRO1071

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to thrombospondin, wherein the polypeptide is designated in the present application as "PRO1071".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1071 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1071 polypeptide having amino acid residues 1 to 525 of Figure 120 (SEQ ID NO:301), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under

high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1071 polypeptide having amino acid residues about 26 to 525 of Figure 120 (SEQ ID NO:301), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA58847-1383 vector deposited on May 20, 1998 as ATCC 209879 which includes the nucleotide sequence encoding PRO1071.

In another embodiment, the invention provides isolated PRO1071 polypeptide. In particular, the invention provides isolated native sequence PRO1071 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 525 of Figure 120 (SEQ ID NO:301). Additional embodiments of the present invention are directed to PRO1071 polypeptides comprising amino acids about 26 to 525 of Figure 120 (SEQ ID NO:301). Optionally, the PRO1071 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA58847-1383 vector deposited on May 20, 1998 as ATCC 209879.

46. PRO1072

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to reductase proteins, wherein the polypeptide is designated in the present application as "PRO1072".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1072 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1072 polypeptide having amino acid residues 1 to 336 of Figure 122 (SEQ ID NO:303), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1072 polypeptide having amino acid residues about 22 to 336 of Figure 122 (SEQ ID NO:303), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA58747-1384 vector deposited on May 14, 1998 as ATCC 209868 which includes the nucleotide sequence encoding PRO1072.

In another embodiment, the invention provides isolated PRO1072 polypeptide. In particular, the invention provides isolated native sequence PRO1072 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 336 of Figure 122 (SEQ ID NO:303). Additional embodiments of the present invention are directed to PRO1072 polypeptides comprising amino acids about 22 to 336 of Figure 122 (SEQ ID NO:303). Optionally, the PRO1072 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA58747-1384 vector deposited on May 14, 1998 as ATCC 209868.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA40210 comprising the nucleotide sequence of Figure 123 (SEQ ID NO:304).

47. PRO1075

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to protein disulfide isomerase, wherein the polypeptide is designated in the present application as "PRO1075".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1075 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1075 polypeptide having amino acid residues 1 to 406 of Figure 125 (SEQ ID NO:309), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1075 polypeptide having amino acid residues about 30 to 406 of Figure 125 (SEQ ID NO:309), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA57689-1385 vector deposited on May 14, 1998 as ATCC 209869 which includes the nucleotide sequence encoding PRO1075.

In another embodiment, the invention provides isolated PRO1075 polypeptide. In particular, the invention provides isolated native sequence PRO1075 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 406 of Figure 125 (SEQ ID NO:309). Additional embodiments of the present invention are directed to PRO1075 polypeptides comprising amino acids about 30 to 406 of Figure 125 (SEQ ID NO:309). Optionally, the PRO1075 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA57689-1385 vector deposited on May 14, 1998 as ATCC 209869.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13059 comprising the nucleotide sequence of Figure 126 (SEQ ID NO:310).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA19463 comprising the nucleotide sequence of Figure 127 (SEQ ID NO:311).

48. PRO181

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the cornichon protein, wherein the polypeptide is designated in the present application as "PRO181".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO181 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO181 polypeptide having amino acid residues 1 to 144 of Figure 129 (SEQ ID NO:322), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO181 polypeptide having amino acid residues about 21 to 144 of Figure 129 (SEQ ID NO:322) or amino acid 1 or about 21 to X of Figure 129 (SEQ ID NO:322) where X is any amino acid from 52 to 61 of Figure 129 (SEQ ID NO:322), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may

comprise the cDNA insert of the DNA23330-1390 vector deposited on April 14, 1998 as ATCC 209775 which includes the nucleotide sequence encoding PRO181.

In another embodiment, the invention provides isolated PRO181 polypeptide. In particular, the invention provides isolated native sequence PRO181 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 144 of Figure 129 (SEQ ID NO:322). Additional embodiments of the present invention are directed to PRO181 polypeptides comprising amino acids about 21 to 144 of Figure 129 (SEQ ID NO:322) or amino acid 1 or about 21 to X of Figure 129 (SEQ ID NO:322), where X is any amino acid from 52 to 61 of Figure 129 (SEQ ID NO:322). Optionally, the PRO181 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA23330-1390 vector deposited on April 14, 1998 as ATCC 209775.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA13242 comprising the nucleotide sequence of Figure 130 (SEQ ID NO:323).

49. PRO195

Applicants have identified a cDNA clone that encodes a novel transmembrane polypeptide, wherein the polypeptide is designated in the present application as "PRO195".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO195 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO195 polypeptide having amino acid residues 1 to 323 of Figure 132 (SEQ ID NO:330), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO195 polypeptide having amino acid residues about 32 to 323 of Figure 132 (SEQ ID NO:330) or amino acid 1 or about 32 to X of Figure 132 (SEQ ID NO:330) where X is any amino acid from 236 to 245 of Figure 132 (SEQ ID NO:330), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA26847-1395 vector deposited on April 14, 1998 as ATCC 209772 which includes the nucleotide sequence encoding PRO195.

In another embodiment, the invention provides isolated PRO195 polypeptide. In particular, the invention provides isolated native sequence PRO195 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 323 of Figure 132 (SEQ ID NO:330). Additional embodiments of the present invention are directed to PRO195 polypeptides comprising amino acids about 32 to 323 of Figure 132 (SEQ ID NO:330) or amino acid 1 or about 32 to X of Figure 132 (SEQ ID NO:330), where X is any amino acid from 236 to 245 of Figure 132 (SEQ ID NO:330). Optionally, the PRO195 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA26847-1395 vector deposited on April 14, 1998 as ATCC 209772.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of Figure 133 (SEQ ID NO:331), herein designated DNA15062.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of Figure 134 (SEQ ID NO:332), herein designated DNA13199.

50. PRO865

Applicants have identified a cDNA clone that encodes a novel secreted polypeptide, wherein the polypeptide is designated in the present application as "PRO865".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO865 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO865 polypeptide having amino acid residues 1 to 468 of Figure 136 (SEQ ID NO:337), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO865 polypeptide having amino acid residues about 24 to 229 of Figure 136 (SEQ ID NO:337), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA53974-1401 vector deposited on April 14, 1998 as ATCC 209774 which includes the nucleotide sequence encoding PRO865.

In another embodiment, the invention provides isolated PRO865 polypeptide. In particular, the invention provides isolated native sequence PRO865 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 468 of Figure 136 (SEQ ID NO:337). An additional embodiment of the present invention is directed to a PRO865 polypeptide comprising amino acids about 24 to 468 of Figure 136 (SEQ ID NO:337). Optionally, the PRO865 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA53974-1401 vector deposited on April 14, 1998 as ATCC 209774.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of Figure 137 (SEQ ID NO:338), herein designated as DNA37642.

51. PRO827

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to integrin proteins, wherein the polypeptide is designated in the present application as "PRO827".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO827 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO827 polypeptide having amino acid residues 1 to 124 of Figure 139 (SEQ ID NO:346), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO827 polypeptide having amino acid residues about 23 to 124 of Figure 139 (SEQ ID NO:346), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the

DNA57039-1402 vector deposited on April 14, 1998 as ATCC 209777 which includes the nucleotide sequence encoding PRO827.

In another embodiment, the invention provides isolated PRO827 polypeptide. In particular, the invention provides isolated native sequence PRO827 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 124 of Figure 139 (SEQ ID NO:346). An additional embodiment of the present invention is directed to a PRO827 polypeptide comprising amino acids about 23 to 124 of Figure 139 (SEQ ID NO:346). Optionally, the PRO827 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA57039-1402 vector deposited on April 14, 1998 as ATCC 209777.

52. PRO1114

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to cytokine receptor family-4 proteins, wherein the polypeptide is designated in the present application as "PRO1114".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1114 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1114 polypeptide having amino acid residues 1 to 311 of Figure 142 (SEQ ID NO:352), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1114 polypeptide having amino acid residues about 30 to 311 of Figure 142 (SEQ ID NO:352) or amino acid 1 or about 30 to X of Figure 142 (SEQ ID NO:352), where X is any amino acid from 225 to 234 of Figure 142 (SEQ ID NO:352), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA57033-1403 vector deposited on May 27, 1998 as ATCC 209905 which includes the nucleotide sequence encoding PRO1114.

In another embodiment, the invention provides isolated PRO1114 polypeptide. In particular, the invention provides isolated native sequence PRO1114 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 311 of Figure 142 (SEQ ID NO:352). Additional embodiments of the present invention are directed to PRO1114 polypeptides comprising amino acids about 30 to 311 of Figure 142 (SEQ ID NO:352) or amino acid 1 or about 30 to X of Figure 142 (SEQ ID NO:352), where X is any amino acid from 225 to 234 of Figure 142 (SEQ ID NO:352). Optionally, the PRO1114 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA57033-1403 vector deposited on May 27, 1998 as ATCC 209905.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA48466 comprising the nucleotide sequence of Figure 143 (SEQ ID NO:353).

A cDNA clone (DNA57033-1403) has been identified that encodes a novel interferon receptor polypeptide, designated in the present application as "PRO1114 interferon receptor".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding

a PRO1114 interferon receptor polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1114 interferon receptor polypeptide having the sequence of amino acid residues from about 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1114 interferon receptor polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 250 or about 337 and about 1182, inclusive, of Figure 141 (SEQ ID NO:351). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209905 (DNA57033-1403) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209905 (DNA57033-1403).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1114 interferon receptor polypeptide having the sequence of amino acid residues from 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, prefereably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1114 interferon receptor polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 29 in the sequence of Figure 142 (SEQ ID NO:352). The transmembrane domain has been tentatively identified as extending from about amino acid position 230 to about amino acid position 255 in the PRO1114 interferon receptor amino acid sequence (Figure 142, SEQ ID NO:352).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1114 interferon receptor polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 141 (SEQ ID NO:351).

In another embodiment, the invention provides a vector comprising DNA encoding PRO1114 interferon receptor or its variants. The vector may comprise any of the isolated nucleic acid molecules hereinabove identified.

A host cell comprising such a vector is also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing PRO1114 interferon receptor polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of PRO1114 interferon receptor and recovering PRO1114 interferon receptor from the cell culture.

In another embodiment, the invention provides isolated PRO1114 interferon receptor polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1114 interferon receptor polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 30 to about 311 of Figure 142 (SEQ ID NO:352).

In another aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352).

In a further aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352).

In yet another aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising the sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or a fragment thereof sufficient to provide a binding site for an anti-PRO1114 interferon receptor antibody. Preferably, the PRO1114 interferon receptor fragment retains a qualitative biological activity of a native PRO1114 interferon receptor polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA

molecule under stringent conditions with (a) a DNA molecule encoding a PRO1114 interferon receptor polypeptide having the sequence of amino acid residues from about 1 or about 30 to about 311, inclusive of Figure 142 (SEQ ID NO:352), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In another embodiment, the invention provides chimeric molecules comprising a PRO1114 interferon receptor polypeptide fused to a heterologous polypeptide or amino acid sequence. An example of such a chimeric molecule comprises a PRO1114 interferon receptor polypeptide fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which specifically binds to a PRO1114 interferon receptor polypeptide. Optionally, the antibody is a monoclonal antibody.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1114 interferon receptor polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1114 interferon receptor antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1114 interferon receptor polypeptide by contacting the native PRO1114 interferon receptor polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1114 interferon receptor polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

53. PRO237

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to carbonic anhydrase, wherein the polypeptide is designated in the present application as "PRO237".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO237 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO237 polypeptide having amino acid residues 1 to 328 of Figure 145 (SEQ ID NO:358), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO237 polypeptide having amino acid residues about 24 to 328 of Figure 145 (SEQ ID NO:358) or amino acid 1 or about 24 to X of Figure 145 (SEQ ID NO:358), where X is any amino acid from 172 to 181 of Figure 145 (SEQ ID NO:358), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA34353-1428 vector deposited on May 12, 1998 as ATCC 209855 which includes the nucleotide sequence encoding PRO237.

In another embodiment, the invention provides isolated PRO237 polypeptide. In particular, the invention provides isolated native sequence PRO237 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 328 of Figure 145 (SEQ ID NO:358). Additional embodiments of the present invention are directed to PRO237 polypeptides comprising amino acids about 24 to 328 of Figure 145 (SEQ ID NO:358) or amino acid 1 or about 24 to X of Figure 145 (SEQ ID NO:358), where X is any amino acid from 172 to 181 of Figure 145 (SEQ ID NO:358). Optionally, the PRO237 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA34353-1428 vector deposited on May 12, 1998 as ATCC 209855.

54. PRO541

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to a trypsin inhibitor protein, wherein the polypeptide is designated in the present application as "PRO541".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO541 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO541 polypeptide having amino acid residues 1 to 500 of Figure 147 (SEQ ID NO:363), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO541 polypeptide having amino acid residues about 21 to 500 of Figure 147 (SEQ ID NO:363), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA45417-1432 vector deposited on May 27, 1998 as ATCC 209910 which includes the nucleotide sequence encoding PRO541.

In another embodiment, the invention provides isolated PRO541 polypeptide. In particular, the invention provides isolated native sequence PRO541 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 500 of Figure 147 (SEQ ID NO:363). Additional embodiments of the present invention are directed to PRO541 polypeptides comprising amino acids about 21 to 500 of Figure 147 (SEQ ID NO:363). Optionally, the PRO541 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA45417-1432 vector deposited on May 27, 1998 as ATCC 209910.

55. PRO273

Applicants have identified a cDNA clone that encodes a novel polypeptide, wherein the polypeptide is designated in the present application as "PRO273".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO273 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO273 polypeptide having amino acid residues 1 through 111 of Figure 149 (SEQ ID NO:370), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally,

under high stringency conditions.

In another embodiment, the invention provides isolated PRO273 polypeptide. In particular, the invention provides isolated native sequence PRO273 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 111 of Figure 149 (SEQ ID NO:370).

56. PRO701

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to neuroligins 1, 2, and 3, wherein the polypeptide is designated in the present application as "PRO701".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO701 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO701 polypeptide having amino acid residues 1 through 816 of Figure 151 (SEQ ID NO:375), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited with the ATCC on March 31, 1998 which includes the nucleotide sequence encoding PRO701.

In another embodiment, the invention provides isolated PRO701 polypeptide. In particular, the invention provides isolated native sequence PRO701 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 816 of Figure 151 (SEQ ID NO:375). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO701 polypeptide. Optionally, the PRO701 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited with the ATCC on March 31, 1998.

57. PRO704

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with VIP36, wherein the polypeptide is designated in the present application as "PRO704".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO704 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO704 polypeptide having amino acid residues 1 through 348 of Figure 153 (SEQ ID NO:380), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 31, 1998 with the ATCC as DNA50911-1288, which includes the nucleotide sequence encoding PRO704.

In another embodiment, the invention provides isolated PRO704 polypeptide. In particular, the invention provides isolated native sequence PRO704 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 348 of Figure 153 (SEQ ID NO:380). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO704 polypeptide. Optionally, the PRO704 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 31, 1998 with the ATCC as DNA50911-1288.

58. PRO706

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to prostatic acid phosphatase precursor and lysosomal acid phosphatase precursor, wherein the polypeptide is designated in the present application as "PRO706".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO706 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO706 polypeptide having amino acid residues 1 through 480 of Figure 155 (SEQ ID NO:385), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 21, 1998 with the ATCC as DNA48329-1290 which includes the nucleotide sequence encoding PRO706.

In another embodiment, the invention provides isolated PRO706 polypeptide. In particular, the invention provides isolated native sequence PRO706 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 480 of Figure 155 (SEQ ID NO:385), or comprising residues 19 through 480 of Figure 155 (SEQ ID NO:385). Optionally, the PRO706 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 21, 1998 with the ATCC as DNA48329-1290.

59. PRO707

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to cadherins, particularly cadherin FIB3, wherein the polypeptide is designated in the present application as "PRO707".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO707 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO707 polypeptide having amino acid residues 1 to 916 of Figure 157 (SEQ ID NO:390), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on May 27, 1998 with the ATCC as DNA48306-1291 which includes the nucleotide sequence encoding PRO707.

In another embodiment, the invention provides isolated PRO707 polypeptide. In particular, the invention provides isolated native sequence PRO707 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 916 of Figure 157 (SEQ ID NO:390). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO707 polypeptide. Optionally, the PRO707 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on May 27, 1998 with the ATCC as DNA48306-1291.

60. PRO322

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to neuropsin, wherein the polypeptide is designated in the present application as "PRO322".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO322 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO322 polypeptide having amino acid residues 1 or 24 through 260 of Figure 159 (SEQ ID NO:395), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 11, 1998 as ATCC no. 209669 which includes the nucleotide sequence encoding PRO322.

In another embodiment, the invention provides isolated PRO322 polypeptide. In particular, the invention provides isolated native sequence PRO322 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 24 through 260 of Figure 159 (SEQ ID NO:395). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO322 polypeptide. Optionally, the PRO322 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 11, 1998 as ATCC no. 209669.

61. PRO526

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with ALS, wherein the polypeptide is designated in the present application as "PRO526".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO526 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO526 polypeptide having amino acid residues 1 to 473 of Figure 161 (SEQ ID NO:400), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 26, 1998 with the ATCC as DNA44184-1319 which includes the nucleotide sequence encoding PRO526.

In another embodiment, the invention provides isolated PRO526 polypeptide. In particular, the invention provides isolated native sequence PRO526 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 473 of Figure 161 (SEQ ID NO:400). Optionally, the PRO526 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 26, 1998 with the ATCC as DNA44184-1319 which includes the nucleotide sequence encoding PRO526.

62. PRO531

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with protocadherins, wherein the polypeptide is designated in the present application as "PRO531".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO531 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO531 polypeptide having amino acid residues 1 to 789 of Figure 163 (SEQ ID NO:405), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 26, 1998 as DNA48314-1320 which includes the nucleotide sequence encoding PRO531.

In another embodiment, the invention provides isolated PRO531 polypeptide. In particular, the invention provides isolated native sequence PRO531 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 789 of Figure 163 (SEQ ID NO:405). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO531 polypeptide. Optionally, the PRO531 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 26, 1998 as DNA48314-1320.

63. PRO534

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with disulfide isomerase (sometimes referred to herein as protein disulfide isomerase), wherein the polypeptide is designated in the present application as "PRO534".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO534 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO534 polypeptide having amino acid residues 1 to 360 of Figure 165 (SEQ ID NO:410), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 26, 1998 as DNA48333-1321 which includes the nucleotide sequence encoding PRO534.

In another embodiment, the invention provides isolated PRO534 polypeptide. In particular, the invention provides isolated native sequence PRO534 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 360 of Figure 165 (SEQ ID NO:410). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO534 polypeptide. Optionally, the PRO534 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 26, 1998 as DNA48333-1321.

64. PRO697

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with sFRPs, wherein the polypeptide is designated in the present application as "PRO697".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO697 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO697 polypeptide having amino acid residues 1 through 295 of Figure 167 (SEQ ID NO:415), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally,

under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited with the ATCC on March 26, 1998 as DNA50920-1325 which includes the nucleotide sequence encoding PRO697.

In another embodiment, the invention provides isolated PRO697 polypeptide. In particular, the invention provides isolated native sequence PRO697 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 295 of Figure 167 (SEQ ID NO:415). Optionally, the PRO697 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited with the ATCC on March 26, 1998 as DNA50920-1325.

65. PRO717

Applicants have identified a cDNA clone that encodes a novel 12 transmembrane polypeptide, wherein the polypeptide is designated in the present application as "PRO717".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO717 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO717 polypeptide having amino acid residues 1 through 560 of Figure 169 (SEQ ID NO:420), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 28, 1998 with the ATCC as DNA50988-1326 which includes the nucleotide sequence encoding PRO717.

In another embodiment, the invention provides isolated PRO717 polypeptide. In particular, the invention provides isolated native sequence PRO717 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 560 of Figure 169 (SEQ ID NO:420). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO717 polypeptide. Optionally, the PRO717 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 28, 1998 with the ATCC as DNA50988-1326.

66. PRO731

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with protocadherin 4, wherein the polypeptide is designated in the present application as "PRO731".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO731 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO731 polypeptide having amino acid residues 1 through 1184 of Figure 171 (SEQ ID NO:425), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on March 31, 1998 with the ATCC as DNA48331-1329 which includes the nucleotide sequence encoding PRO731.

In another embodiment, the invention provides isolated PRO731 polypeptide. In particular, the

invention provides isolated native sequence PRO731 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 1184 of Figure 171 (SEQ ID NO:425). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO731 polypeptide. Optionally, the PRO731 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on March 31, 1998 with the ATCC as DNA48331-1329.

67. PRO218

Applicants have identified a cDNA clone that encodes a novel multi-transmembrane protein having sequence identity with membrane regulator proteins, wherein the polypeptide is designated in the present application as "PRO218".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO218 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO218 polypeptide having amino acid residues 1 through 455 of Figure 173 (SEQ ID NO:430), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 28, 1998 with the ATCC as DNA30867-1335 which includes the nucleotide sequence encoding PRO218.

In another embodiment, the invention provides isolated PRO218 polypeptide. In particular, the invention provides isolated native sequence PRO218 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 455 of Figure 173 (SEQ ID NO:430). Optionally, the PRO218 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 28, 1998 with the ATCC as DNA30867-1335.

In another embodiment, the invention provides an expressed sequence tag (EST) sequence comprising the nucleotide sequence of Figure 174 (SEQ ID NO:431), designated herein as DNA14472.

In another embodiment, the invention provides an expressed sequence tag (EST) sequence comprising the nucleotide sequence of Figure 175 (SEQ ID NO:432), designated herein as DNA15846.

68. PRO768

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with integrins, wherein the polypeptide is designated in the present application as "PRO768".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO768 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO768 polypeptide having amino acid residues 1 through 1141 of Figure 177 (SEQ ID NO:437), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 6, 1998 as DNA55737-1345 which includes the nucleotide sequence encoding PRO768.

In another embodiment, the invention provides isolated PRO768 polypeptide. In particular, the invention provides isolated native sequence PRO768 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 1141 of Figure 177 (SEQ ID NO:437). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO768 polypeptide. Optionally, the PRO768 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 6, 1998 as DNA55737-1345.

69. PRO771

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with testican, wherein the polypeptide is designated in the present application as "PRO771".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO771 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO771 polypeptide having amino acid residues 1 through 436 of Figure 179 (SEQ ID NO:442), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 7, 1998 with the ATCC as DNA49829-1346 which includes the nucleotide sequence encoding PRO771.

In another embodiment, the invention provides isolated PRO771 polypeptide. In particular, the invention provides isolated native sequence PRO771 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 436 of Figure 179 (SEQ ID NO:442). Optionally, the PRO771 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on April 7, 1998 with the ATCC as DNA49829-1346.

70. PRO733

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with the T1/ST2 receptor binding protein, wherein the polypeptide is designated in the present application as "PRO733".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO733 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO733 polypeptide having amino acid residues 1 through 229 of Figure 181 (SEQ ID NO:447), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on April 7, 1998 with the ATCC as DNA52196-1348 which includes the nucleotide sequence encoding PRO733.

In another embodiment, the invention provides isolated PRO733 polypeptide. In particular, the invention provides isolated native sequence PRO733 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 229 of Figure 181 (SEQ ID NO:447). An additional embodiment